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OCTOBER 1954

VOLUME 52 NUMBER 4

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

TABLE OF CONTENTS FIRST PAGE

a scientific corner

FOR INFORMAL DISCUSSION OF YOUR OPTICAL PROBLEMS

The House of Vision Inc.

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ON SELECTING TRIFOCALS

Ophthalmologists are prescribing trifocals much more freely than they did a few years back. We are very much in favor of this trend because well fitted and well selected trifocals do a real job and give the wearers optical comfort they never dreamed possible. When failures occur they are usually due either to poor fitting or, more often, to poor selection.

A well known and widely used line of flat top trifocals may be ordered with either a 6 mm. or an 8 mm. intermediate segment. A study of a number of patients who were not too happy about these trifocals leads us to believe that the fault was in the selection and not in the trifocal. Doctor F., a physician, requires the following prescription: Right $-2.00 + 0.50 \times 80$; Left $-1.75 + 0.37 \times 100$, with a $+ 2.00$ add for reading and a $+ 1.00$ intermediate add. He was given trifocals with 6 mm. intermediate segments and was not a bit satisfied with the results. 8 mm. segments were made for him and found to be perfectly satisfactory.

Mr. B. was given 8 mm. intermediate segments on the following prescription: Right $+ 0.50 + 0.75 \times 90$; Left $+ 0.75$ cylinder $\times 90$, with a $+ 3.00$ reading add and a $+ 1.50$ intermediate add. The results were not satisfactory until we made a new pair of trifocals with 6 mm. segments. This pair did the trick nicely.

The conclusion arrived at from these and other cases is that when the reading addition is $+ 2.75$ or $+ 3.00$, or when the patient has poor accommodation, use the 6 mm. segment. Using the narrower segment gives a larger reading field and puts it higher in relation to the eye.

The patient requiring a $+ 1.75$ or $+ 2.00$ add likes the 8 mm. seg because he can use the intermediate portion for a surprising percentage of his visual tasks. The reading segment being lower does not handicap him, as he uses it only occasionally.

The person who requires a $+ 3.00$ add is usually well along in years and while the intermediate segment is a valuable adjunct the acuity through this portion just isn't as good as through the reading segment.

"if it's a lens problem, let's look at it together"

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TABLE OF CONTENTS

ORIGINAL ARTICLES

PAGE

Normal Vitreous, Its Attachments and Dynamics During Ocular Movement
A. C. Hilding, M.D., Ph.D., Duluth, Minn. 497

Oxyphenonium (Antrenyl)
William H. Havener, M.D., and Harold F. Falls, M.D., Ann Arbor, Mich. 515

Oxyphenonium (Antrenyl), a Substitute for Atropine
Ira A. Abrahamson Jr., M.D., Cincinnati, and Paul Hurwitz, M.D., Chicago 519

Factors Involved in Several Tests of Binocular Depth Perception
Louise L. Sloan, Ph.D., and Adelaide Altman, A.B., Baltimore 524

Cortisone in Lens Discission and Extracapsular Extraction
Robert L. Smith, B.A.; R. M. Fasanella, M.D.; E. Rosenthal, M.D., and T. E. Hoffman, New Haven, Conn. 545

Perimeter with Controlled Illumination and Recording Mechanism
Morgan B. Raiford, M.D., D.Sc.(Med.), Atlanta, Ga. 550

Streptokinase-Streptodornase (Varidase) in Treatment of Corneal Ulcers
Captain Almerindo G. Portfolio, Medical Corps, United States Army Reserve 557

A New Camera for Medical Stereophotography with Special Reference to the Eye
David D. Donaldson, M.D., Boston 564

Effect of Changes in Osmotic Pressure of Blood on Aqueous Humor Dynamics
Andrew de Roetth Jr., M.D., New York 571

Diagnostic Value of Foveal Entoptic Phenomena in Glaucoma
Ingeborg Schmidt, M.D., Bloomington, Ind. 583

REGISTRY OF INTERESTING CASES

Plexiform Neurofibroma of Orbit and Lid with Defects in Walls of Orbit and Involvement of Central Nervous System
Joseph A. Sabri, M.D., and Alfred Diab, M.D., F.A.C.S., F.I.C.S., Beirut, Lebanon .. 598

ANNUAL REVIEWS

Physiologic Chemistry of the Eye
Ludwig von Sallmann, M.D., New York 604

SOCIETY TRANSACTIONS

New York Academy of Medicine, Section of Ophthalmology 641

REGULAR DEPARTMENTS

News and Comment 653

Books 654

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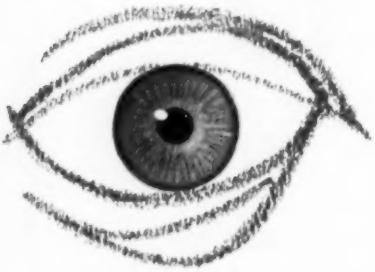

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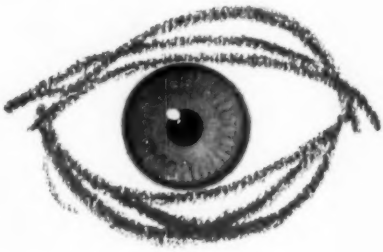

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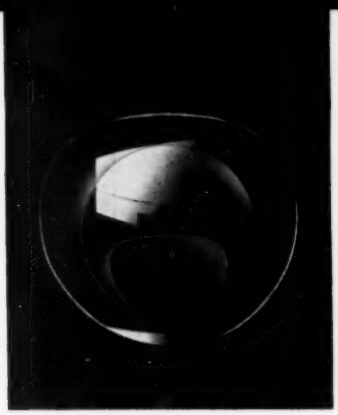
1. Gettes, B. C., and Leopold, I. H.: A. M. A. Arch. of Ophth. 49:24 (Jan.) 1953.
2. Stolzar, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.



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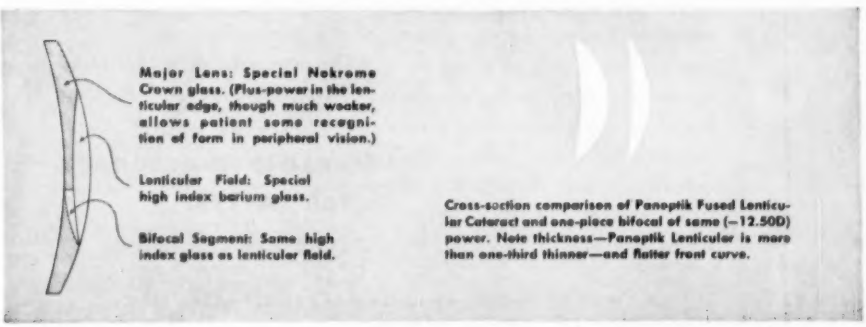
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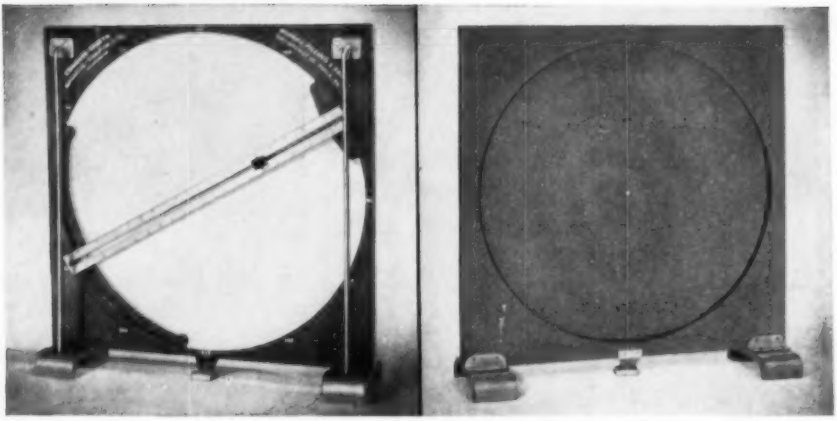

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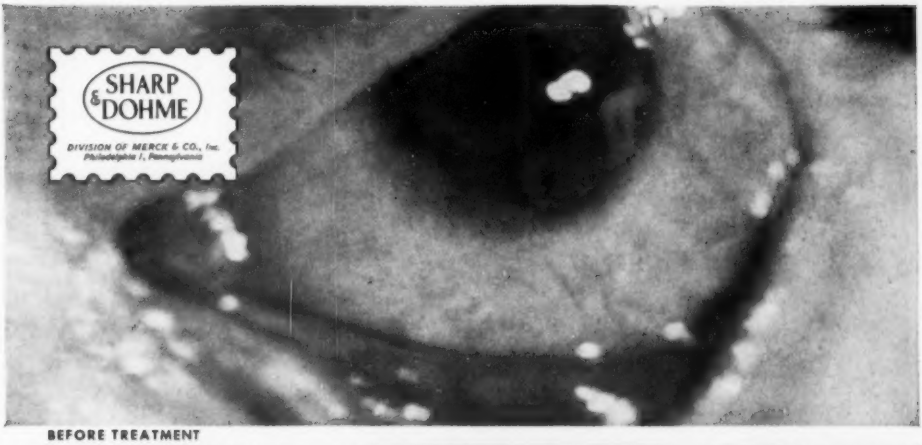

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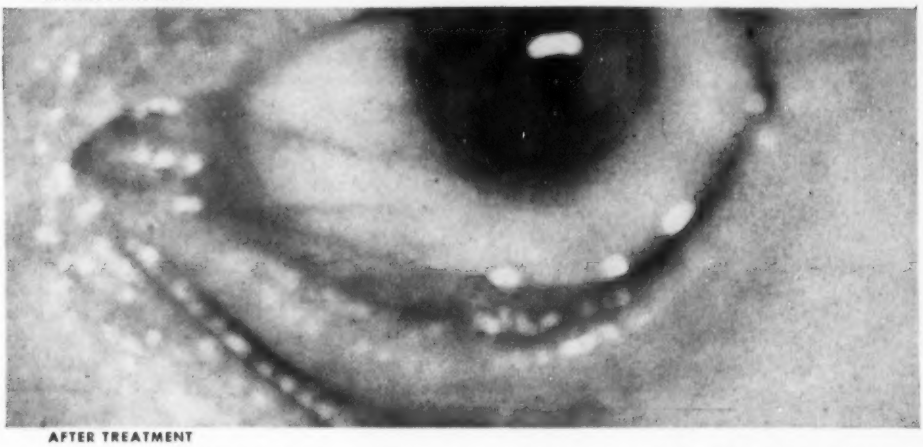

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1. Harrison, W. J.: Ocular Therapeutics, Springfield, Ill., Charles C Thomas.

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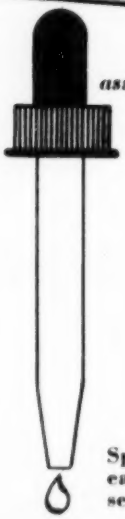

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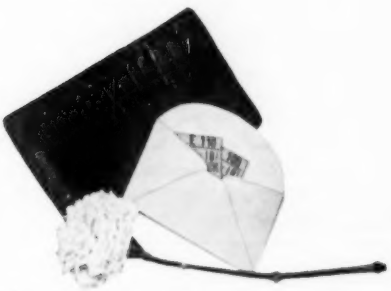

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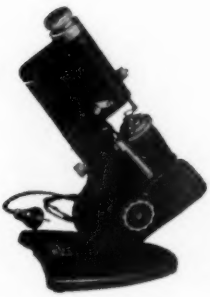

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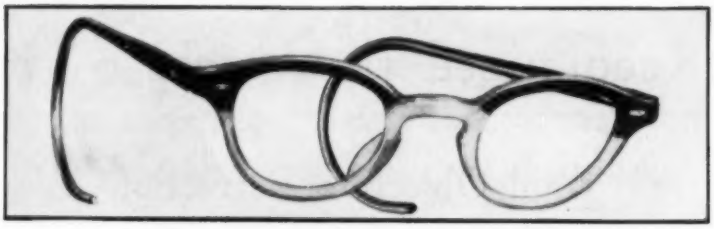

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VOLUME 52 OCTOBER 1954 NUMBER 4

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NORMAL VITREOUS, ITS ATTACHMENTS AND DYNAMICS DURING OCULAR MOVEMENT

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THERE HAVE been many studies on the vitreous body; yet it is incompletely understood. It undoubtedly plays a large role in ocular pathology and in the complications after ocular surgery. The present study is an attempt to visualize and analyze the physiologic movements of the vitreous during ocular rotations.

The anatomic characteristics and relations of the vitreous are difficult to ascertain because of its transparency and its perishable nature. Numerous studies have been made during the past century, the results of which are not uniform; in fact, the conclusions in some respects are rather contradictory and confusing. Best,[7] who made an outstanding anatomic study nearly 50 years ago, was aware of a relation of the vitreous to retinal detachment, and his concept of the vitreous structure seems to be rather close to that which is presently held. Among the more recent excellent contributions are those of Friedenwald and Stiehler,[14] Grignola,[16] Irvine,[18] Pirie,* Bembridge and associates,[3] and Pischel.[2]

EXTERNAL FEATURES AND ATTACHMENTS

Some features are fairly well established. The vitreous is surrounded by a hyaloid membrane, which is firmly incorporated with its substance. Grignola [16] could not separate it from the underlying structure; Cowan and Fry † did so in some of the lower animals and photographed it as an anatomic entity. Some have denied the existence of a membrane at all, stating that there is only a surface condensation of a colloidal gel (Mann,[21] Duke-Elder,[13] Anderson,[1] and Berens [5]). The controversy over the hyaloid membrane seems to be as much a matter of definition of the term "membrane" as it is a difference of opinion. From the standpoint of the physical behavior of the surface of the vitreous, there certainly is a membrane. From the standpoint of histology, there may be some question whether one means by "membrane" a separate, discrete, two-sided structure which is formed, or has been produced as such, by cells.

The vitreous body is attached to the surrounding structures in several areas. Its chief attachment is at the so-called base. This is a ring 2 or 3 mm. wide, extending from the ora serrata forward onto the pars plana of the ciliary body.‡ This attachment is firm and is reinforced in the substance of the vitreous by a ring of increased

Presently working in the Research Laboratory at St. Luke's Hospital, under grants from the Louis W. and Maud Hill Family Foundation of St. Paul, the Women's Service Guild of St. Luke's Hospital, Miss Elisabeth Congdon, and The Edward C. Congdon Memorial Trust.

* References 24 and 25.

† References 9 and 10.

‡ References 16 and 18.

density. When attempts are made to separate this attachment, parts of the epithelium of the ciliary processes tear away from these structures and remain attached to the base of the vitreous body. There is a second ring-like attachment to the lens capsule, which is known as Eggers' line (Fig. 1), and a third, or smaller, ring attachment at the optic disc, which is about the size of the latter. A still smaller attachment is present at the macula. In general, the vitreous is attached to firm tissue other than the retina or is attached to the retina where this, in turn, is attached to deeper, firmer

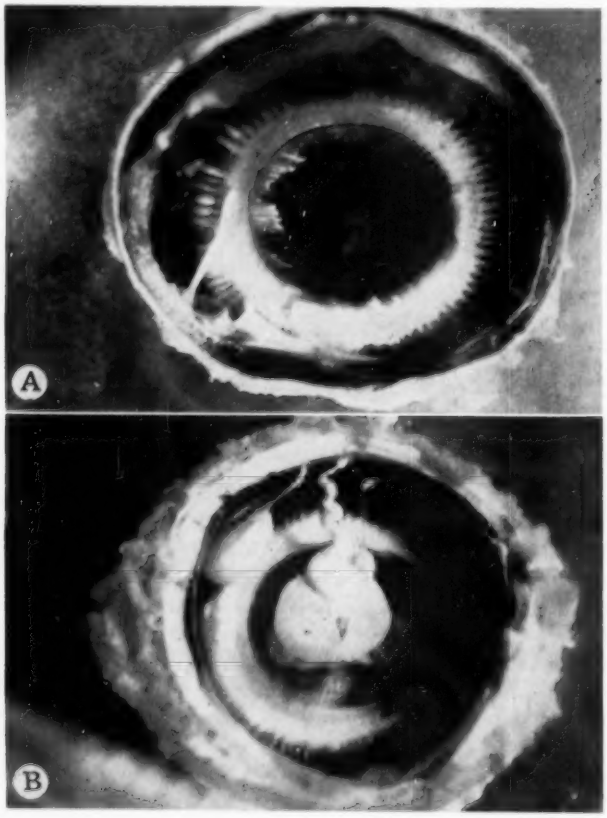


Fig. 1.—*A*, anterior half of an ox eye which had been bisected at the equator, as seen from the plane of section. The region of the zonule was injected with white ink, which flowed freely, forming the corona about the lens, as seen. A small amount passed to the anterior surface of the lens, and is visible on the left side and above. The streak far to the left marks the track of the needle through the vitreous body.

B, anterior half of another ox eye in which two injections were made, the first into the retrolental space, just anterior to the vitreous. This injection formed a very thin, saucer-like plaque, seen on the center of the lens. The dark triangle in the center of the plaque is a tear in the hyaloid membrane made by the point of the needle. The thick spiral above the plaque was caused by leakage of ink from the retrolental space along the track of the needle after the latter was withdrawn. The second injection was made into the zonular region. An insufficient amount of ink to fill this space was used. When the needle was withdrawn, the ink continued to flow into the unfilled portion. The dark line between the zonular corona and the plaque in the retrolental space marks the attachment of the vitreous to the lens capsule. This attachment in man is called Eggers' line.

tissue. On the whole, it seems to be free from the retina in that large extent where the two layers of the embryonic optic vesicle lie in apposition but unattached to each other (retina and its pigment epithelium). Yet there are weaker attachments described at the equator [16] and at some other points [12]; and, judging by the location of retinal tears, there must be still others in some persons. The secondary vitreous is produced by retinal cells in embryonic life and for a time is attached to the retina [22] over the entire surface of the latter. It is quite possible that remnants of these embryonic connections remain into adult life, as do remnants of the pupillary membrane. (Pathologic adhesions from chorioretinitis, of course, occur.) Ruptures in some of the normal vitreous attachments are seen clinically not so infrequently; these result in detachment of the vitreous body. The ring-like attachment at the disc is especially apt to tear free.[2] It is the attachment at the macula, presumably, which causes destructive traction in vitreous complications following cataract surgery.[18]

INTERNAL FEATURES

According to modern concepts, the vitreous has a definite internal structure and is not merely a colloid gel, a view held by Salgado Benevides [4] and Duke-Elder.[13] Friedenwald and Stiehler [14] found concentric layers, which fused together at intervals, forming flat, concentric cells. Grignola [16] recently reported an extensive study consistent with Best's fibrillar concept. Grignola concluded that there is a definite net-like, fibrillar structure extending throughout the entire vitreous body. It originates at the base in bundles that split into fine fibrils; these branch and anastomose with one another to form a complete net-like framework. He identified three kinds of fibrils, all of which have a certain amount of elasticity. Chemical studies have been made of these fibrils by Bembridge [3] and Matoltsy [23] and their co-workers, Pirie,§ and others, indicating that they are not chemically identical. Grignola does not seem to consider the internal structure as separated into two units corresponding to primary and secondary vitreous.

Thus, the modern concept of the vitreous is that of an anatomic unit with a definite internal structure lying within the retina, and firmly attached to the surrounding structures at the base and less firmly attached at a number of other points.

A search of the literature reveals few reports analyzing movements of the vitreous ‖; yet these movements and the forces which bring them about are doubtless of great importance in a number of disease conditions, including detachment of the retina and postoperative complications of intraocular surgery. A study of these forces might be fruitful in a better understanding of pathologic conditions of the vitreous and retina, and possibly in their prevention and treatment.

EXPERIMENTAL STUDIES OF NORMAL MOVEMENTS

Some attempts were made to study the vitreous movements in ox eyes during rotation. Freshly enucleated eyes were mounted on a wire frame, as illustrated (Fig. 2*A* and *B*), with strong silk sutures at 12 and 6 o'clock, thus creating a fixed vertical axis. Rubber bands were stitched in at 3 o'clock and 9 o'clock and put on a slight stretch horizontally. Long silk threads were also attached at 3 o'clock and 9 o'clock, by means of which the eye could be turned out of position and the rubber

§ References 24 and 25.

‖ References 7 and 22.

bands put on stretch. When the threads were released, the rubber bands would rotate the eye back into position. Sometimes it was found advantageous not to let go of the threads but to ease the eye back, as it were. Two windows were cut through the sclera for the purpose of admitting light and for observation, as illustrated (Fig. 2*B*). The sclera, choroid, tapetum, and retina were dissected off successively and carefully so as not to damage the hyaloid.¶ White ink was injected into various

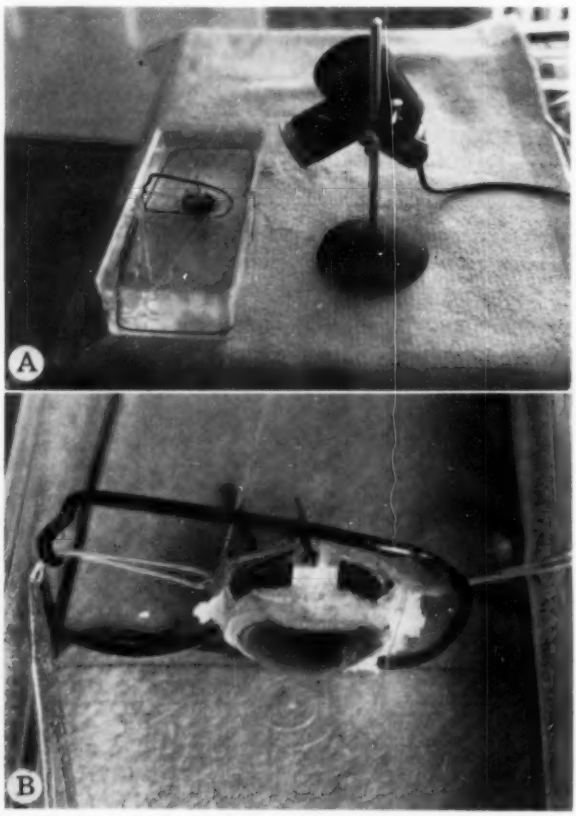


Fig. 2.—Method of mounting (*A*) and dissection (*B*) of an ox eye for the rotation experiment, as described in the text.

positions in the vitreous by means of a hypodermic needle, and the movements of this ink were observed as the eye rotated.

Result.—It was found that the vitreous in these ox eyes was much firmer than the human vitreous. The ox eye is not spherical but is flattened markedly in an anteroposterior direction. For these reasons, the movements were quite different

¶ During these dissections it was found that the anterior attachment of the vitreous at the base was so firm and strong that the ciliary body and iris were badly torn in attempting to separate it. The attachment at the optic nerve was so weak that it separated easily during the manipulations incidental to dissection.

than those observed in the human eye with a slit lamp. There was none of the free-flowing postrotational movement that is so characteristic of the anterior part of the human vitreous. The movements were shorter, more rapid, and almost bouncing. Figure 3 illustrates the movement of a streak across the vitreous a short distance behind the lens, as seen from above. The ink streak assumed an *S* form at the end of rotation. The greatest bend did not occur midway between the center and the sclera but was closer to the center. The bend was considerably greater on the side where the movement was away from the lens rather than toward it. The movement in the posterior part of the vitreous was studied in a vertical direction. As the eye

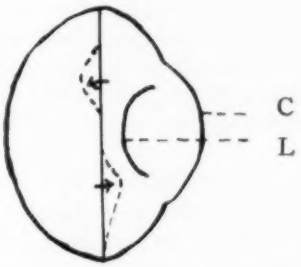


Fig. 3.—Diagrammatic representation of movement during rotation of a streak of ink placed horizontally across the vitreous behind the lens. Solid line indicates ink before rotation; dotted line, ink immediately upon cessation of rotation; *C*, corneal surface; *L*, posterior lens surface.

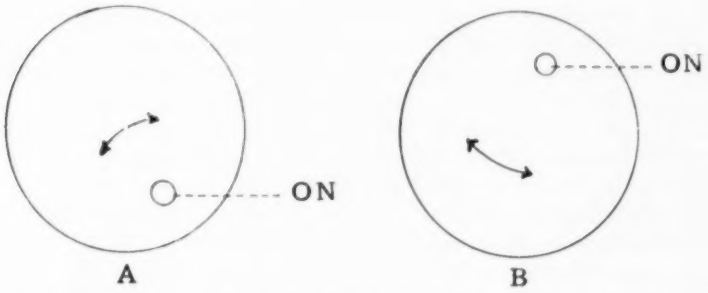


Fig. 4.—Diagrammatic representation of a blob of ink in the posterior vitreous during rotation on a vertical axis (*A*) with the eye in normal position and the optic nerve (*ON*) in the lower outer quadrant, and (*B*) with the eye upside down and the optic nerve in the upper outer quadrant. The ink behaved as though it were suspended from the optic nerve. The relation of this behavior to the optic nerve may have been more seeming than real, as explained in the text.

was rotated about the vertical axis, the inertial lag did not occur horizontally, as one might expect. Rather, the movements seemed to center at and rotate about the optic nerve. When the ox eye is in a normal position, the optic nerve is in the lower outer quadrant. In this position, a blob of white ink placed in the posterior vitreous bobbed back and forth on an arc centering at or near the optic disc. The movement was reminiscent of the movements of the metronome which my daughter uses during piano practice. When the eye was suspended upside down, so that the disc was in the upper outer quadrant, the movements gave the impression that the blob of ink was suspended from a point at or near the disc, as on a swing. These observations

made it appear as though the posterior vitreous rotated more or less about the attachments at the disc (Fig. 4 *A* and *B*). However, when another eye was bisected through the equator and the vitreous in the posterior half observed, this did not seem to be the case at all. In fact, in the particular eye treated this way, the rotation seemed to center at or near the posterior pole. It may be, of course, that the attachment at the disc was ruptured during dissection. Another streak of ink, which was placed near the cut surface of the vitreous hemisphere, gave the impression that there was an attachment eccentrically in the cut surface (the division across the vitreous was not exactly on the equator, and part of the thickened ring at the base was included on one side).

These observations raise an important consideration in one's mind, since they would indicate that the bobbing or rotational movements observed in the vitreous of the ox eye may be due in part, and perhaps in large part, to the internal structure rather than to the external attachments. The seeming rotation about the disc may or may not have been related to the attachments at this point.

FORCES INVOLVED IN MOVEMENT

Relative movements between the vitreous and the structures which contain it occur when the eye rotates. The formula expressing the tangenital force used in rotating a sphere in the absence of friction is

$$F = 2/5\ M \times R \times A$$

where the force (F) is expressed in dynes, the mass (M) in grams, the radius (R) in centimeters, and the acceleration (A) in radians per second squared. Considering that the eye rotates at the average rate of 300 degrees per second,[26] and probably attains a maximum velocity of 600 degrees per second, it follows that in order to accelerate a sphere, such as the eye, to that maximum velocity, a tangential force of 0.6 gm. would be required.# The force required to rotate the wall of the eye, sclera, and cornea, without the contained vitreous and lens, would be about 0.6 of the total force, considering that the wall is 1 mm. thick and roughly one-fourth of the total weight. The force would be applied on the outside of the sclera by the extraocular muscles. However, such mathematical formulas scarcely express the conditions involving the vitreous. The vitreous is not a solid sphere; it is loosely constructed and when rotated shows a very definite tendency, from inertia and friction, to lag in its various parts. The force required to rotate it is somewhere between that required to rotate the wall alone and that required to rotate a solid sphere the size of the eye. At any rate, force is required to rotate the vitreous, and that force is applied through its attachments to the surrounding structures. If some of these attachments should be dissolved through disease, then greater force would fall upon those which remained. Likewise, if the internal structures were altered in such a way that lines of tension were produced, through shortening or tearing parts of the network, again, it is conceivable that the brunt of the torsional forces would fall much more strongly upon some attachments than others. If remnants of embryonic attachments remain or if abnormal ones develop through adhesions, torsional forces might be brought to bear upon the retina or other structures, at points which are not designed to sustain such force, resulting in ruptures and tears.

Any good physics textbook may be consulted, such as that of Hausmann and Slack.[27]

SLIT LAMP OBSERVATIONS—MOVEMENTS OBSERVED

Slit lamp observations were made through the pupils of many phakic eyes, and sketches made of 64, in order to study the movements of that portion of the vitreous which is readily available to the slit lamp. A general pattern of movement was found in most normal eyes, although there were numerous variations. The technique for observation was very simple: With the patient fixing some portion of the corneal microscope, the slit and microscope were focused upon some visible feature in the anterior portion of the vitreous. The patient was then directed to look at the examiner's finger held some 20 to 30 degrees toward the nasal side. After the gaze was held in this position a moment, the patient was directed to look back at the original point of fixation. This movement from the finger back to the original position was the rotation studied. Immediate observation was made upon the direction and extent of the movements in the vitreous after cessation of rotation. The motion during rotation of the eye, of course, was not observed, only the postrotational movement. If a difference between the movements of primary and secondary vitreous exists, this also was not observed.

Several points of interest were immediately apparent. First, the movement does not suggest that of a firm gel; rather, it appears to be a somewhat loose and flowing one, through which the rotational forces are made effective by some type of internal structure. There is a very striking progressive lag from the posterior lens capsule back toward the center, which causes a wave of movement affecting the vitreous close to the lens first and that near the center last. A whip-like traveling wave passes through the vitreous from before backward. A settling movement follows.

Thus, the most usual pattern of postrotational movements includes two phases: (1) a rapid, horizontal flowing movement in the direction of rotation, the duration of which is about 1½ seconds (as determined by the stop watch), and (2) a slow, settling movement, which lasts from 7 to 15 seconds. The first, or primary, movement usually has a rather high velocity by the time the eye has fixed and rapidly decelerates until it stops, in from one to two seconds. The closer to the anterior surface the observer focuses his microscope, the more closely the primary movement follows the wall of the eye. The farther back he looks, the greater the lag. One receives the impression that there must be a structural arrangement within the vitreous substance which is both slack and elastic. As the slack is taken up progressively from before backward, rotational movement begins from before backward in a whip-like traveling wave (Figs. 5 and 6). One would judge by the action that the structural elements also stretch somewhat, snapping the visible elements forward as the structure shortens again. In the horizontal plane, there seems to be no residual change of position of the various portions of the vitreous relative to the wall of the globe. They appear to rotate to their original prerotational position in the circle. They even overshoot a trifle, as evidenced by the small reverse correctional movement in the second, or settling, phase. Damping is rapid and is almost aperiodic and critical. The overshoot is minimal, as though the viscosity were great.

The second phase, or settling movement, begins immediately after the first and is, generally speaking, at right angles to the first. The visible elements settle by gravity, as in a viscid fluid. The duration of this movement is from 7 to 15 seconds, and the velocity grows progressively less until it is scarcely perceptible and finally

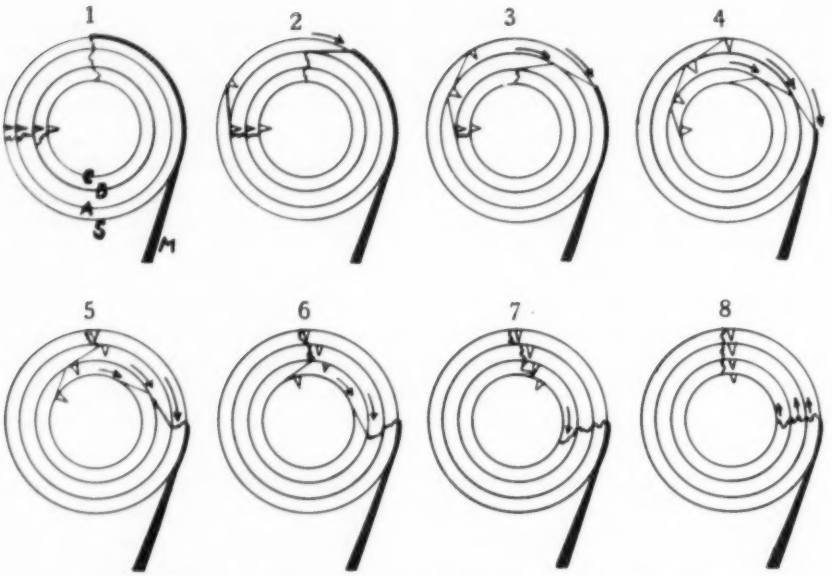
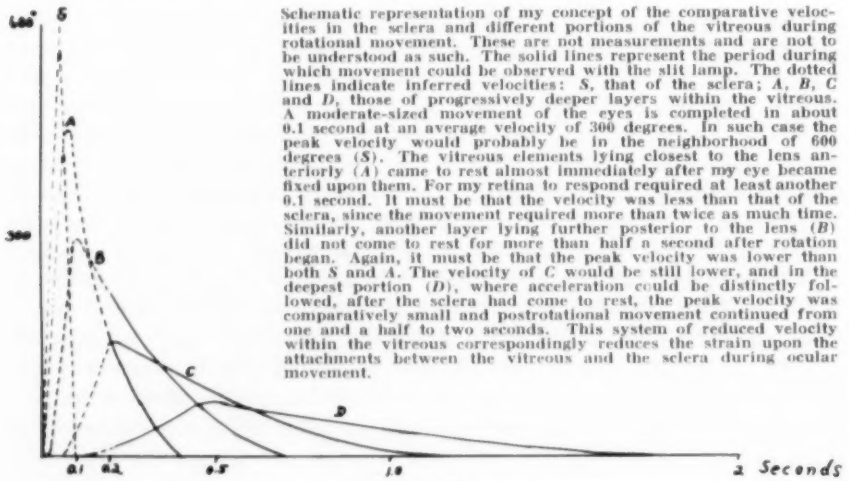


Fig. 5.—Schematic representation of the system of slack and lag in the vitreous. The outer circle (*S*) represents the sclera, and *A*, *B*, and *C* indicate progressively deeper layers within the vitreous. As the strap *M* (representing a rectus muscle) rotates circle *S*, there is a latent period before circle *A* begins to move, during which the slack between *S* and *A* is taken up. There is an additional latent period before circle *B* begins to move, during which the slack between *A* and *B* is taken up. The same applies to *C*. When all the slack has been taken up and all the circles are rotating, the strain of the attachments to the outer circle reaches a maximum. When the strap ceases to pull, the outer circle (*S*) comes to rest, while the circles *A*, *B*, and *C*, because of their momentum, continue to rotate. Each in turn comes to rest as it is damped down by internal friction. In the vitreous, there is a small overshoot, as in *7*, which is corrected, as in *8*, in such manner that when all movement is over, the elements are in the same relative position as before movement was begun. (This representation is not intended to indicate that the vitreous is necessarily constructed in concentric layers.)



Schematic representation of my concept of the comparative velocities in the sclera and different portions of the vitreous during rotational movement. These are not measurements and are not to be understood as such. The solid lines represent the period during which movement could be observed with the slit lamp. The dotted lines indicate inferred velocities: *S*, that of the sclera; *A*, *B*, *C* and *D*, those of progressively deeper layers within the vitreous. A moderate-sized movement of the eyes is completed in about 0.1 second at an average velocity of 300 degrees. In such case the peak velocity would probably be in the neighborhood of 600 degrees (*S*). The vitreous elements lying closest to the lens anteriorly (*A*) came to rest almost immediately after my eye became fixed upon them. For my retina to respond required at least another 0.1 second. It must be that the velocity was less than that of the sclera, since the movement required more than twice as much time. Similarly, another layer lying further posterior to the lens (*B*) did not come to rest for more than half a second after rotation began. Again, it must be that the peak velocity was lower than both *S* and *A*. The velocity of *C* would be still lower, and in the deepest portion (*D*), where acceleration could be distinctly followed, after the sclera had come to rest, the peak velocity was comparatively small and postrotational movement continued from one and a half to two seconds. This system of reduced velocity within the vitreous correspondingly reduces the strain upon the attachments between the vitreous and the sclera during ocular movement.

Figure 6

ceases entirely. This settling movement would indicate a slackness of the supporting structure. The downward movement is often inclined slightly back (away from the direction of rotation), as stated, as though there had been a slight overshoot which is being corrected (Fig. 5). The downward falling movement is quite constantly present. It must follow that there has been a previous upward movement. Pre-

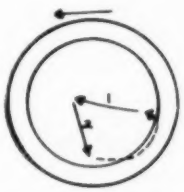


Fig. 7. Approximate path of a particle lying in the anterior lower vitreous during and after a short rotation in the direction indicated by the arrow above the circles. The inner circle represents the margin of the dilated pupil. The dashed arrow indicates the inferred movement relative to the globe during rotation; this cannot be observed by the methods used in this study. Arrows *1* and *2* represent the direction and extent of the first and second phases of postrotational movement after the globe has come to rest. The duration of the first phase is about 1.5 seconds, and that of the second phase, roughly 10 seconds.

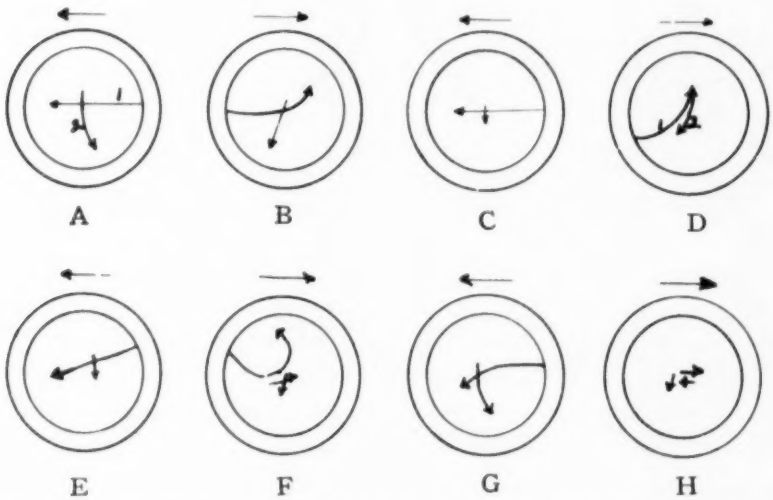


Fig. 8.—Normal patterns of postrotational flow or movement of the anterior portion of the vitreous as observed through the corneal microscope and slit lamp. *A* and *B*, from a 63-year-old man and an 18-year-old woman, respectively, are the common forms seen. *C* and *D* indicate movements, respectively, in the right and left eyes of a 42-year-old man. The first phase in the right eye was about horizontal and of rather wide amplitude, whereas in the second phase, that of settling, the movements had a small excursion. In the left eye, the first phase flowed as much upward as in the direction of rotation. The settling phase was greater than in the right eye. The pattern in a given eye seems to be constant with a given rotation. *E* and *F* are the patterns observed in the right and left eyes, respectively, of a 42-year-old woman. The first phase in the right eye was very rapid and of rather wide amplitude. The second was of small excursion. In the left eye both phases were short close behind the lens, as though the vitreous were attached there, whereas further posterior there was a spiral flow, as indicated by the longer arrow. *G* shows a free-flowing first phase with a downward direction and a long second phase (man, aged 73). (*H*) In the left eye of a 52-year-old woman, a very brief, short first phase with a rebound was observed. The second phase was also short. This vitreous must have been firmer than usual or the visible elements must have been firmly attached to the lens and ciliary body.

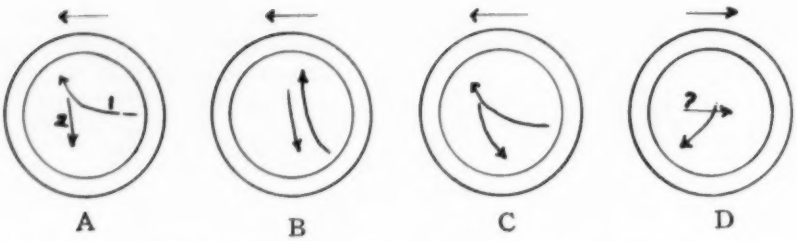


Fig. 9.—Patterns found in myopic persons: *A*, myopia of 2.25 D., shows a common type of movement; *B*, myopia 2 D., exhibits an unusual first phase in that it is almost straight upward. Both these patterns were in young women. In *C* the movements were perhaps somewhat freer-flowing than usual but were otherwise ordinary, despite the fact that this eye had myopia of 9.50 D. In *D* (—4.25 sph. ⌒ 1.50 cyl.) the first phase was so rapid that it could not be followed with certainty. A centripetal deflection from the posterior surface of the lens was noted.

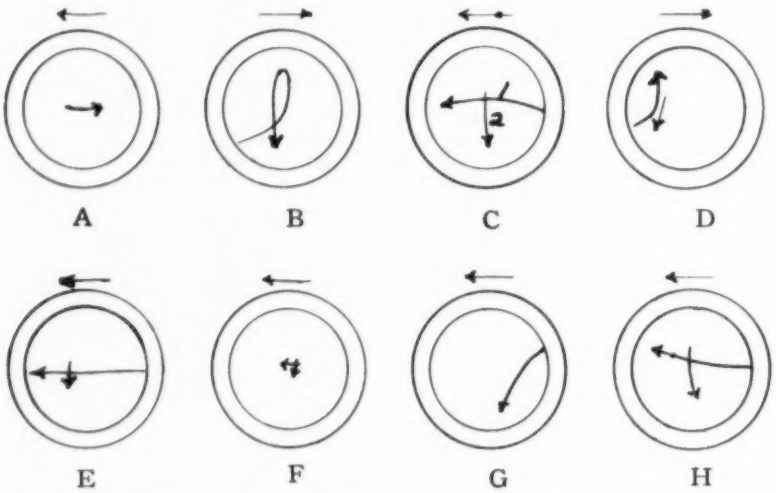


Fig. 10.—Patterns found in some abnormal eyes. *A*, pattern in a case of microphthalmos. The postrotational movement was short and rapid and in a direction the reverse of the rotation. *B*, pattern found in heterochromic cyclitis. The flow was in the form of a spiral directed upward and forward. That this unusual pattern was related to the heterochromia is doubtful, because a similar symmetrical pattern was found in the normal fellow eye. *C* and *D* are from the right eye rotating to the right and left, respectively, in a 40-year-old man. This eye was struck by an arrow during childhood, and the lens subluxated medially. The first phase, after right rotation, was free-flowing and almost horizontal, whereas after left rotation movement was snubbed sharply before reaching the center and was deflected upward, as though meeting an obstruction which was not visible. *E*, an eye which had been twice operated on for retinal detachment, with mechanical success. The first phase was wide and free-flowing, giving the impression of a near-liquid state. The second phase was short and slow. *F*, exophthalmos due to an orbital tumor (neurolemmoma at the apex, subsequently removed). The unusually short excursion of both phases was probably not due to the tumor. *G*, pattern found in a case of congenital cataract (age 32), and *H*, pattern in a vitreous filled with asteroid bodies. In *H* the movements were not especially unusual, but they could be very well observed.

sumably, this takes place during the rotation of the eye and must be upward and in the reverse direction from that of the rotation. It is so rapid that it is completed by the time the eye comes to rest in fixation (Fig. 7).

Both phases of postrotational movement vary in rate; the firmer the vitreous, the more rapid the primary following movement; the more liquid, the greater the lag—at least this is the impression one receives. The downward secondary movement is always much slower than the primary, but this rate also varies considerably among individual eyes. Individual variations are illustrated in Figures 8, 9, and 10. I made some observations on my own muscae and found the movements to be very similar to those found in the eyes of patients (Fig. 11).

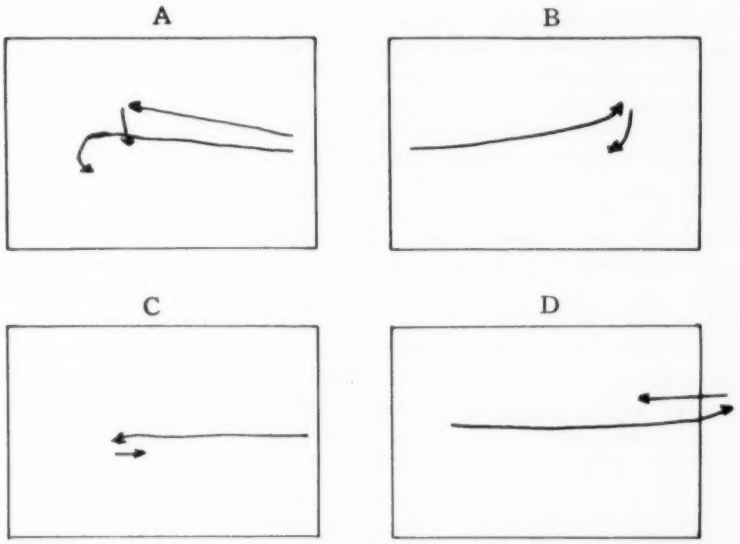


Fig. 11.—Movements of the muscae in my right eye: *A* and *B*, movements in horizontal left and right rotation, respectively. In left rotation, there was a spiral downward movement of some of the shadows, not shared by all. *C* and *D*, movements in left and right rotation while looking downward at a sheet of paper.

TRANSMISSION OF FORCES

Thus far, in the discussion, no mention has been made of other possible routes of transmission of rotational force to the vitreous than through its external attachments and internal structure. There are other routes, namely, the convex posterior surface of the lens, which lies in the patellar fossa, and internal friction or viscosity.

In a physical system consisting of a viscid or gelatinous mass, enclosed within a sphere, but unattached to that sphere, any flattened or protuberant (internal) area on the wall of the sphere would aid in imparting motion to the mass as the enclosing sphere is rotated. The vitreous fits accurately within the enclosing spherical sclera. The lens constitutes a convex area upon the inner surface of the enclosing sphere. (Relative to the vitreous through its zonular attachments, the lens actually is a part of the enclosing wall.) Through its posterior convexity, the lens thus has a sort of grip or hold upon the vitreous, by means of which it can impart

rotational forces to the latter quite independently of any attachments. After rotation of the globe has ceased and the vitreous continues to rotate in the postrotational movement, the convexity of the lens has a damping effect.

Once the surface of the vireous has begun to rotate, the torsional forces are transmitted progressively deeper into the vitreous by internal friction or viscosity, as well as by the slack and elastic internal structure.

Consider the interplay of forces which are involved at a point on the equator laterally at 3 o'clock when the left eye is rotated from a position 25 degrees nasally to the primary position. The velocity of the movement imparted to the wall of the eye by the extraocular muscles is in the magnitude of 300 degrees per second.[13] However, that is the average velocity. At its high point in the middle of the movement, the velocity is doubtless at least twice that. Hence, the acceleration of the wall is very rapid. On the other hand, the vitreous begins to move only after a brief latent period, during which there is a slight relative horizontal movement between the wall and the surface of the vitreous. Then the surface layer of the vitreous (hyaloid membrane) begins to move. This, in turn, is followed by angular acceleration in the layers of the vitreous immediately beneath the hyaloid, and this, in turn, by angular acceleration in each successively deeper layer until the center is reached. The rotational force is imparted to the hyaloid membrane at the radius under consideration through the pull of the attachments at the macula and disc (and equator, if any). It is even likely that the pull is transmitted all the way from the base of the vitreous at 9 o'clock on the opposite medial side of the eye, past the disc and macula, and then anteriorly to the point under consideration. (It is scarcely conceivable that the attachment of the base at 3 o'clock could impart force to the hyaloid, at the point under consideration, by pushing, but the denser ring just within the base may act by pushing.) The rotating force is then carried from the hyaloid membrane progressively into the deeper layers through a pull on the structural framework as the slack in this is progressively taken up. Thus, angular acceleration is imparted to the whole vitreous (Figs. 5 and 6).

The torsional force acting upon the vitreous attachments would be greatest at that moment when the inertia and internal friction of the vitreous offer the greatest resistance to the angular acceleration. That point would come at or before the greatest velocity is reached.* When rotation ceases and the eye fixes again, the relative motion between the wall and the vitreous reverses in direction. Deceleration begins immediately in the vitreous. In fact, at the hyaloid membrane deceleration begins practically at the same time as that in the wall of the eye, which would probably be somewhere near the midpoint in the arc of rotation. Deceleration would continue in the various layers of the vitreous progressively from the outside toward the center until, at the end of one or two seconds, the deepest parts have come to rest as far as following horizontal movement is concerned. (In the deeper layers of the vitreous the change from acceleration to deceleration does not occur at the midpoint in time of the rotational arc because the rate of acceleration imparted by the pull on the internal structure is greater than the rate of deceleration imparted by internal friction during the floating movement of deceleration [Fig. 6]). During postrotational movement, there is undoubtedly a pull on the attachments beween the vitreous

* There are some centrifugal forces involved, especially when the velocity is high, but they are probably not of much significance.

and the wall, due to the momentum in the moving vitreous. However, the pull or tug on these attachments in deceleration would never be as great as during acceleration because the internal friction which resisted acceleration, thereby increasing the pull on the attachments, would act to assist in the deceleration, thus decreasing the pull on the attachments necessary to bring the vitreous to rest. The effect of the impact and deflection at the lenticular convexity would serve to dampen the post-rotational movement further. Hence, if any damage were ever done at the points of attachment of the vitreous, as presumably happens when the retina tears preliminary to detachment, that damage would occur during acceleration.

POINTS OF GREATEST STRAIN

It should be possible in a very general way now to locate the points of greatest strain upon the vitreous attachments during rotation if the known attachments are considered. Given a medial rotation of the left eye, the movement of the anterior vitreous relative to the lens during acceleration would be directed laterally. The force of the inertial sag or lag of the vitreous mass located between the disc and the ora would fall upon the attachments at the medial equator, the base of the medial

Measurement on Three Preserved Human Eyes and on One Fresh Eye Between the Optic Nerve and the Limbus

	Average Measurements Preserved Eyes, Mm.	Average Measurements Fresh Eye, Mm.
Lateral	31	38
Medial	25.7	26
Superior	29.6	34
Inferior	28	30

ora, the medial aspect of the convexity of the lens and Eggers' line (where a change of direction would be imparted), the lateral side of Eggers' line, the lateral base, and the lateral equator. The attachments on the lateral side of the center of the lens would be partially protected from the full force of the flow by the convexity of the lens, which would impart to the vitreous a centripetal acceleration with a damping influence. The full force would fall upon the attachments medial to the lens, and if any damage resulted in medial rotation, it would be on the medial side. Similarly, the greatest force in lateral rotation would fall upon the attachments lateral to the lens, and if damage should occur it would be here.

The distance between the optic nerve and the limbus is greater on the lateral side of the eye than on the medial side and is greater above, at 12 o'clock, than below, at 6 o'clock (Table). These differences would be even greater between the disc and the equator. Presumably the spatial relations between the disc and the basal attachment of the vitreous are similar, and hence the vitreous mass on the lateral side, between the disc and the ora, should be greater than that on the medial side, and it should be greater above than below. There is a vitreous attachment at the disc and a smaller one at the macula. These attachments are weaker than the anterior ones but, as long as they are intact, must serve like the others to impart rotational force from the wall of the eye to the vitreous and would relieve the attachments at the equator and in the anterior segment of a portion of the rotational force. Because

of the eccentric position of the disc on the medial side of the posterior pole, the relief of strain upon the equatorial and anterior attachments afforded by the attachment at the disc would be greater on the medial than the lateral side, and greater below than above. Hence, other factors being equal, the strain upon the equatorial and anterior attachments would be greater in lateral than in medial rotation, and greater in upward than in downward gaze. Another factor which would make the strain greater above than below is the fact that the slack in the internal vitreous structure (where it can be visualized anteriorly) gravitates toward the bottom of the eye. As the eye rotates upward, the strain comes first upon the upper vitreous structure and later upon the lower, as the slack is taken up.

Considering all these facts, other factors remaining equal, the greatest strain upon the anterior and equatorial vitreous attachments should come during acceleration in lateral rotation, and the point of maximum strain would be located some-

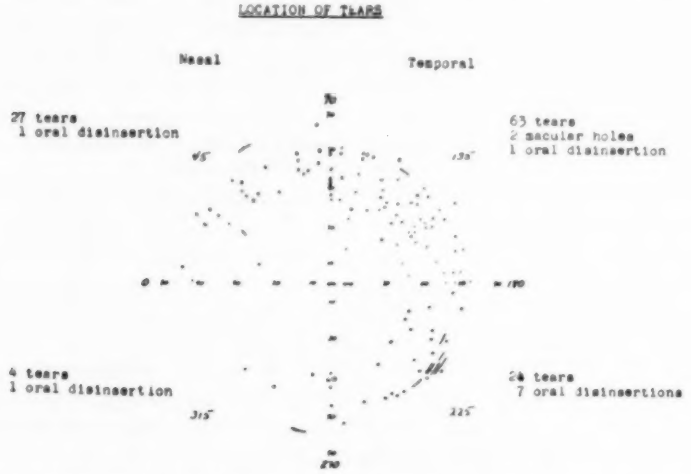


Fig. 12.—Distribution of tears found by Appleby and Pischel [2] in 100 cases of retinal detachment. Each dot represents a tear. It will be observed that most are in the upper outer quadrant. (Consent was obtained from the author and from the editor of the *American Journal of Ophthalmology* to reproduce this illustration.)

where in the upper lateral quadrant. One cannot, of course, assume that other factors are equal. The likelihood is that the attachments at Eggers' line, the base, and the equator are not symmetrically placed or of equal extent and strength on the medial and lateral sides. Such asymmetries in strength and position would be significant, as would the action of the attachment at the macula. Moreover, tears are not necessarily confined to normal attachments. They may be caused by abnormal attachments.

Nevertheless, as a matter of fact, our thesis would appear to be essentially correct, as indicated by the distribution of retinal tears. More retinal tears occur laterally than medially and in the upper half of the eye than the lower. The center of the greatest incidence is in the upper outer quadrant (Fig. 12).[2] The U- and V-shaped tears are usually oriented with the apex of the tear directed posteriorly and the base anteriorly, and the vitreous attachment which caused the tear is found

on the anterior lip.[19] This indicates that at the moment of tear the vitreous was moving anteriorly, i. e., toward the lens. If the greatest strain occurs during acceleration, that would mean that the wall of the eye at the tear was moving backward. Tears in the lateral part of the retina would, therefore, occur during acceleration of lateral rotation and tears in the medial part during acceleration of medial rotation.

SUMMARY

The vitreous is attached to the wall of the eye in a number of areas. The largest and strongest is a circular band just anterior to the ora serrata. This attachment is variously known as the base or the vitreoretinal symphysis. There is another ring of attachment to the lens capsule, known as Eggers' line, and there is a ring at the disc and a small attachment at the macula. In addition, weaker attachments in the region of the equator and anterior to it, whether normal or abnormal, are usual. These last attachments are important. As the eye rotates in the ordinary movements associated with vision, torsional forces are applied to the vitreous through its attachments, causing the vitreous to rotate also. Owing to its inertia, the movements of the vitreous lag behind those of the wall of the eye. The loose character of the structure of the vitreous and its viscid nature make these internal movements more or less characteristic. The velocity of the eye movements, i. e., cornea and sclera, is comparatively high, and these movements consist of two phases—acceleration and deceleration. The velocity is greatest at about the middle of the rotational movement, when acceleration ceases. Through its attachments, the vitreous accelerates also, but only after a short latent period, during which the slack in its internal structure is taken up. This latent period increases progressively from the hyaloid membrane toward the center. The strain upon the attachments would presumably be greatest about the time of the highest velocity in the wall of the eye, at which point the pull on the attachments would be due to the inertial resistance of that part of the vitreous already set in motion plus the internal friction. Early in deceleration of the wall of the eye, the pull upon these attachments would cease momentarily and then, as the momentum of the revolving vitreous carried it along in the direction of rotation, the pull would be resumed, but in the reverse direction, and the vitreous also would begin to decelerate. The pull upon the attachments during deceleration would consist in the force necessary to bring the vitreous to rest minus the damping of internal friction and minus the damping influence of the convex posterior surface of the lens. Moreover, the time of deceleration is much greater than that of acceleration, another factor which would reduce the forces involved in deceleration. Therefore, the greatest strain would always come during acceleration in any movement.

The elements in the anterior vitreous which can be visualized by the slit lamp move along rather characteristic pathways, which have wide normal variations among individual subjects, but which for a given eye seem to be quite constant. The vitreous movement during rotation of the sclera is so rapid that one cannot follow it, but one can infer its character. The anterior portion of the primary vitreous hangs suspended, as it were, upon drapes which are attached above and are slack below. As the eye rotates, force is applied first to the attachments above, from which the "drapes" are hanging, and the lower portions of the vitreous swing upward in relative counterrotation. The movement is similar to that which would be imparted to a child's swing if the supports were suddenly projected forward. The postrotational movements, i. e., after the sclera has come to rest, can be seen

very well. By the time the eye comes to rest and the observer has fixed his eye on the vitreous, he finds it streaming by the posterior surface of the lens in the direction of rotation, more or less horizontally. This motion ceases in from one to two seconds, after which another motion begins immediately, namely, a settling toward the bottom, with typically a slight counterrotational inclination, as though there had been a small amount of overshoot. The damping is critical, and there is usually no oscillation and comparatively little overshoot. This second phase of postrotational movement may continue from 7 to 15 seconds.

The distance on the surface of the vitreous between the disc and the ora serrata is greater on the lateral than on the medial side. Hence, one would expect a greater mass of vitreous to sag against the anterior and equatorial attachments during lateral rotation than during medial rotation. Similarly, one would expect a greater inertial sag against the anterior and equatorial attachments during upward gaze than in downward gaze. By virtue of the fact that the vitreous structure hangs as though suspended from above, one would expect greater force due to inertia of the vitreous to be applied above than below in all directions of gaze unless it be downward. Considering all these factors, the greatest strain during ordinary daily use of the eyes would come upon the vitreous attachments in the upper outer quadrant. If this is true, then, other factors being equal, most retinal tears of the vitreous type should occur in the upper outer quadrant. Other factors are probably not equal; nevertheless, it is true that most tears occur in the upper outer quadrant. This would indicate that it is the minor attachments, whether normal or abnormal, rather than the major ones, which cause retinal tears, with the exception of disinsertion. The vitreous attachment which causes any given tear is found on the anterior lip of the tear, and when the tear is U-shaped or V-shaped, the base lies anteriorly. This would indicate that the tear occurred when that portion of the wall of the eye was moving backward and the vitreous had a relative forward movement.

The effect of the eccentric position of the disc on the distribution of tear may be due to the internal structural arrangement as much as to the actual attachment at that point, as indicated by the experiments on the ox vitreous.

Thus, we find that there is a great difference in the acceleration and velocity of the shell of the eye, as contrasted with the gelatinous interior, which difference appears to be purposeful. The optical system and the retina are an integral part of, or attached rigidly to, this outer shell, which composes one-fourth of the mass of the eye. The movements of the optical system and the retina must be sufficiently rapid to avoid visual impression. When the eye is rotated from one position to another, there is no visual impression. Such movements consume 0.1 second or less. The acceleration and velocity involved are high. It is not necessary that the gelatinous vitreous (three-fourths of the mass of the eye) move so rapidly. Through a device of slack and lag in the internal structure of the vitreous, the time involved in rotation is increased 10 to 20 times over that of the retina and sclera. The force at the attachments has been correspondingly reduced. The work of moving the vitreous is accomplished, but, because of the increased period of time, the necessary forces involved are very greatly diminished. This protects the vitreous attachments from undue strain in the numerous, sudden, jerky movements incident to the daily use of the eyes.

If significant differences exist between the movements of the primary and those of the secondary vitreous, these were not observed in this study.

CONCLUSIONS

1. The rotation of the visible vitreous during eye movements presents three aspects: the first, during rotation of the eye, in which the anterior portion of the vitreous moves upward and in relative counterrotation; the second, or first postrotational phase, during which the vitreous flows rapidly in the direction of rotation, and the third, or second postrotational phase, in which it settles slowly downward and slightly back into the bottom of the eye.

2. The torsional force applied through the vitreous attachments would be greater during acceleration than deceleration and greatest about the time the velocity reaches its highest point and the inertial drag of the vitreous is greatest.

3. The greatest strain upon the anterior and equatorial vitreous attachments normally would seem to be in the upper outer quadrant.

4. The system of loose structure within the vitreous permits of slack and lag, which greatly reduce the acceleration and velocity of the vitreous as compared with those of the sclera and retina during eye movements. This device of slack and lag diminishes the amount of necessary force to which the vitreous attachments are subjected.

Dr. Howard Hanson, of the Physics Department of the University of Minnesota, Duluth Branch, assisted in working out the mathematical and physical formulae, and the Elliott Packing Company, of Duluth, provided me with the material used in the experimental study.

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OXYPHENONIUM (ANTRENYL)

A Potent Atropine Substitute

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OXYPHENONIUM (Antrenyl), a synthetic quaternary ammonium salt (diethyl [2-hydroxyethyl] methylammonium bromide α-phenylcyclohexaneglycolate), is a powerful mydriatic and cycloplegic drug. Its anticholinergic pharmacologic effects are essentially the same as those of atropine and are obtainable with approximately the same concentration of drug.[1] Oxyphenonium is stable in tablet or solution and may be administered topically, orally, or parenterally. It is freely soluble in water and almost completely insoluble in nonpolar solvents. Oxyphenonium has been used clinically in the therapy of peptic ulcer and allied digestive disorders [2] and as a preanesthetic medication.

LABORATORY EVALUATION OF OXYPHENONIUM

Excellent mydriasis, persisting for four to eight days, is produced in adult albino rabbits by a single ocular instillation of one drop of 5% oxyphenonium bromide in 1 : 5,000 benzalkonium (Zephiran) chloride. This mydriasis is complete within an hour. A 1% oxyphenonium solution produces complete mydriasis for two days, with return to normal by the fifth day. Table 1 presents results obtained with a single instillation of 0.5% oxyphenonium bromide in 1 : 5,000 benzalkonium chloride in 30 rabbit eyes. Two-thirds of the eyes showed complete mydriasis for one day, then gradually returned to normal by the fourth day. For comparison, Table 2 depicts the action of 1% atropine in 1 : 5,000 benzalkonium chloride on eight rabbit eyes. Six of the eight eyes were never completely dilated, and within 24 hours all pupils were normal. Comparison of Tables 1 and 2 would seem to indicate that 0.5% oxyphenonium is much more potent than 1% atropine —this contrast cannot be carried over directly to humans, however, because many herbivora, including rabbits, have a species characteristic permitting them to detoxify belladonna alkaloids at a greater rate than do humans.

The oxyphenonium-dilated rabbit iris is refractory to the miotic action of 0.05% diisopropyl fluorophosphate in peanut oil or of 2% pilocarpine hydrochloride in 1 : 5,000 benzalkonium chloride. Twenty-two rabbit pupils were dilated with one drop

Ciba Pharmaceutical Products, Inc., Summit, N. J., supplied the Antrenyl used in this project.

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of 0.5% oxyphenonium bromide in 1 : 5,000 benzalkonium chloride. Four hours later, and again five hours after the oxyphenonium instillation, a drop of diisopropyl fluorophosphate was placed in one eye of each rabbit. Nine of the 11 eyes so treated were uninfluenced by the miotic, as judged by the paired, control eye. Two of the 11 pupils so treated had returned to normal size by seven hours and were still normal at all subsequent observations. In repeating the above experiment with 2% pilocarpine hydrochloride, it was observed that the oxyphenonium mydriasis was uninfluenced in all 11 rabbits.

In rabbits, despite a very severe iritis, ocular instillation of 5% oxyphenonium in 1 : 5,000 benzalkonium chloride once daily maintained excellent mydriasis and prevented secondary complications (16 eyes). This was proved during the course of a study to evaluate the action of specific antifungicides in controlling anterior seg-

TABLE 1.—*Reaction of Rabbit Eyes to Single Drop of 0.5% Oxyphenonium Chloride* *

	Start	4 Hours	One Day	Two Days	Three Days	Four Days	Five Days
No light	..	30	22	1	..	..	..
Slight light	..	..	8	24	6	..	..
Moderate light	..	..	..	5	21	7	..
Good light	30	..	..	..	3	20	7

* The figures represent the number of rabbit eyes showing the given degree of pupillary reaction to light at the stated time.

TABLE 2.—*Reaction of Rabbit Eyes to Single Drop of 1% Atropine* *

	Start	4 Hours	One Day	Two Days	Three Days	Four Days	Five Days
No light	..	2	..	..	..	..	..
Slight light	..	1	..	..	..	..	..
Moderate light	..	5	..	..	..	..	..
Good light	8	..	8	..	..	..	..

* The figures represent the number of rabbit eyes showing the given degree of pupillary reaction to light at the stated time.

ment ocular infection with Sporotrichum schenckii. (Untreated ocular sporotrichosis produced a virulent, destructive iridocyclitis with secondary complications serious enough to destroy functionally seven of eight rabbit eyes.)

In all rabbits, repeated instillation of 5% oxyphenonium (daily for several months during several experiments) did not produce injurious ocular effects. The drug was apparently irritating in 5% concentration, producing transient conjunctival exudation shown microscopically to consist of polymorphonuclear leucocytes in a fibrinous matrix. This ocular irritation and exudation was occasionally present with the use of 1% solutions, but never with 0.5%.

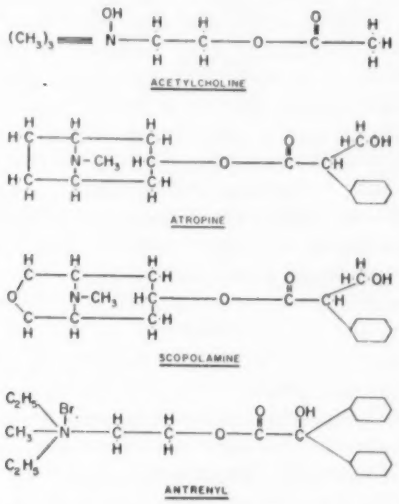
No rabbit showed any allergic response to oxyphenonium.

CLINICAL EVALUATION OF OXYPHENONIUM

It is relatively difficult to assess the value of a potent atropine substitute clinically. The disability of prolonged cycloplegia discourages volunteers and precludes the use of refraction patients. The degree of individual mydriasis varies markedly after ocular surgery, in iridocyclitis, and in other pathologic conditions requiring mydriatic therapy. Cycloplegic effects are likewise not readily studied in diseased eyes.

The antigenic behavior of topically applied drugs is, however, easily determined. P. J. (University of Michigan Hospital, #753686) was a postoperative cataract patient with typical severe atropine sensitivity. Change of medication from 1% atropine to 0.5% oxyphenonium resulted in prompt subsidence of symptoms. Good mydriasis was maintained, and no evidence of sensitivity to oxyphenonium developed during the two weeks of postoperative therapy with oxyphenonium. Twelve patients with marked ocular atropine sensitivity have been treated with oxyphenonium. Not one patient exhibited cross sensitivity to oxyphenonium, nor did any develop oxyphenonium allergy during the course of therapy. Mydriasis was adequate in all, and the primary pathologic state followed the expected course.

After cataract surgery, 14 patients were treated with oxyphenonium, 1% in 1 : 5,000 benzalkonium chloride, one drop daily. Additional medication with 10%



Molecular structure of acetylcholine, atropine, scopolamine, and oxyphenonium (Antrenyl).

phenylephrine (Neo-Synephrine) hydrochloride and 1% oxyphenonium bromide ointment was considered advisable in approximately two-thirds of these patients to secure the desired mydriasis. Three patients did not have adequate dilation with the oxyphenonium-phenylephrine regime, and the therapy was changed to 1% atropine. In one of these three patients the pupil dilated better with atropine, but the other two showed no increased response. It was concluded that 1% oxyphenonium, one drop daily, did not produce quite as consistent a mydriasis as that effected by atropine in similar dosage. Oxyphenonium therapy was definitely adequate when supplemented as indicated by 1% oxyphenonium ointment and 10% phenylephrine solution at the time of the daily postoperative dressing. (Atropine mydriasis also commonly requires supplementation by 1% atropine ointment and 10% phenylephrine.

In the three patients in whom 1% oxyphenonium was used as a cycloplegic, the drug was found to be essentially comparable to atropine. This finding is in agree-

ment with that of Hurwitz,* who reports that in clinical use 5% oxyphenonium produces prolonged cycloplegia and mydriasis without untoward effects or appreciable irritation.

A 1% or a 0.5% solution of oxyphenonium chloride in 1 : 5,000 benzalkonium chloride was not irritating to the human eye. It is our belief that a 1% solution is optimal because it produces the desired effect and is not strong enough to cause smarting or conjunctival discharge. Furthermore, a single drop of a 5% solution contains more than 3 mg. of potent drug—whether atropine or oxyphenonium, a dose sufficient to produce oral dryness, constipation, and possibly urinary difficulty in a susceptible elderly patient.

COMMENT

Parasympatholytic drugs are effective by virtue of their resemblance to the parasympathetic effector substance acetylcholine. They are chemically similar enough to form a combination with the end-organ as would acetylcholine, but are not susceptible to destruction by cholinesterase and therefore "block" the end-organ. The accompanying Figure clearly illustrates the similarity between acetylcholine and anticholinergic compounds. The essential structure is apparently the esterification of an organic acid with an amine base. It is striking how great a pharmacologic difference may be made by only a small change of the molecular configuration. Specifically, scopolamine differs from atropine only in having an oxygen bridge between two carbon atoms, and thereby is antigenically changed enough to permit its use in atropine sensitivity. Synthetic anticholinergic compounds, such as oxyphenonium, are much more unlike the atropine molecule than is scopolamine, and yet retain the required basic similarity to acetylcholine.

SUMMARY

Oxyphenonium (Antrenyl) is a synthetic, long-acting, potent anticholinergic drug. In rabbits the mydriatic effect of oxyphenonium is very much more marked and prolonged than that of atropine; however, the rabbit can detoxify belladonna drugs much more rapidly than can man. Oxyphenonium mydriasis in rabbits is resistant to the effect of diisopropyl fluorophosphate and pilocarpine.

Clinical evaluation indicates that oxyphenonium is satisfactory for use in cases of atropine sensitivity. No cross sensitivity between these two drugs was observed in 12 cases of atropine allergy. The effect of 1% oxyphenonium bromide in 1 : 5,000 benzalkonium chloride is practically comparable in degree and duration to that of 1% atropine, and these two drugs may be used interchangeably in ophthalmic therapy.

Dr. Irving Shapiro, Dr. Robert Kobs, and Dr. William Roberts helped in the preparation of this paper.

* Hurwitz, Paul: Personal communication to the authors.

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OXYPHENONIUM (ANTRENYL), A SUBSTITUTE FOR ATROPINE

A Clinical Study

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THE CONSTANT search for new synthetic mydriatic and cycloplegic drugs as substitutes for homatropine and atropine continues to stimulate the investigator. Most recently, cyclopentylate (Cyclogyl) [1] and its allied chemicals * have met with some degree of success as short-acting cycloplegic replacements for homatropine.

Other similar-acting agents,[5] whose initial effectiveness proved illusory, have, however, attained limited, though valuable, purposes in the ophthalmological armamentarium. Several such drugs are hydroxyamphetamine (Paredrine), phenylephrine (Neo-Synephrine), eucatropine (Euphthalmine), and Dibutoline.[6]

There is no adequate long-acting synthetic cycloplegic substitute for atropine. Only BL 139 [7] (β-β-diphenyl-γ-dimethylaminovaleramide) approaches the efficacy of atropine in its autonomic ganglion-blocking action and its cycloplegic-mydriatic effect. However, it has not been made available.

Oxyphenonium (Antrenyl), as a potential substitute for atropine, came to our attention during the clinical study of its systemic administration, because of its side-reactions—dryness of the mouth and pupillary dilation. The prolonged cycloplegic and mydriatic action of this drug became immediately apparent after ocular instillation.

Oxyphenonium is a synthetic quaternary compound, structurally related to adiphenine (Trasentine) hydrochloride. It is crystalline and easily soluble in water, with a neutral reaction. Chemically, it is diethyl-(2-hydroxyethyl)-methylammonium bromide-α-phenylcyclohexaneglycolate.

Oxyphenonium is used as an antispasmotic and autonomic ganglion-blocking agent in the treatment of peptic ulcer and in spastic disorders of the gastrointestinal and urinary tracts. Its spasmolytic action, exceeding that of atropine, renders it valuable in the treatment of bronchial spasm.

PHARMACOLOGY

Laboratory results prove oxyphenonium to be anticholinergic, a strong pilocarpine antagonist, and an autonomic ganglion-blocking agent. Bronchial spasm

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The Antrenyl was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.
From the Eye Department of the Cook County Hospital and Chicago Medical School.
* References 2, 3, and 4.

and salivation, normally induced by pilocarpine, are completely allayed by the systemic administration of minute doses of oxyphenonium. Likewise, spasm of the uterus of the guinea pig, stimulated by pilocarpine, can be prevented, as well as terminated, by oxyphenonium. The strong anticholinergic effect of oxyphenonium is demonstrated by the complete cessation of small intestine spasm caused by acetylcholine. Oxyphenonium also abolished the effect of acetycholine in stopping the beat of the isolated heart.

Salivation and pupillary dilation normally follow electrical stimulation of the preganglionic cervical sympathetic fibers. Oxyphenonium injected intra-arterially, through a branch of the lingual artery, acts as a ganglionic block and results in a suppression of these responses. Faradization of the postganglionic fibers of the cervical sympathetic nerve results in a restitution of the salivation and pupillary dilation.

CLINICAL STUDIES

Oxyphenonium was prepared for experimental use as a 5% ophthalmic solution, in isotonic saline and also in several buffered solutions. Despite the various vehicles used, the drug caused a moderate burning sensation and occasionally a

TABLE 1.—*Mydriasis*

Age, Yr.	Race	Onset, Min.	Completion, Min.	Degree, Mm.	Duration, Days
31	W	22	50	7.5	19
25	W	35	55	8.0	18
14	N	35	60	7.5	18
30	W	25	80	8.0	10
30	N	30	55	6.5	10
42	W	25	60	8.0	21
29	N	30	60	7.5	18
Average		22-35	50-80	6.5-8.0	10-21

conjunctival secretion. One drop of a topical anesthetic preceding instillation of the oxyphenonium eliminated the burning.

Primarily, this study is concerned with the mydriatic and cycloplegic effect of oxyphenonium. A secondary noteworthy aspect is the reaction in patients allergic to atropine.

Mydriasis.—Twenty adult patients were studied especially for mydriasis. After one drop of 5% oxyphenonium bromide solution, the pupil commenced dilating in 15 to 35 minutes and was dilated maximally within 37 to 80 minutes. This dilation was slightly wider than with atropine and persisted for 10 to 21 days, in eyes of white persons and Negroes alike. The results for seven of these patients are cited in Table 1.

Cycloplegia.—In the same group of 20 patients the cycloplegic effect of oxyphenonium was studied. Cycloplegia commenced in 20 to 45 minutes, following one drop of 5% oxyphenonium bromide solution, and was complete in 40 to 90 minutes. The residual accommodation was determined by measuring the near point after correcting the distant refractive error. The residual accommodation after oxyphenonium was +0.50 to +1.50 D. This finding compares favorably with a residual accommodation of +0.50 to +1.75 D. after atropinization. The cycloplegia persisted from 7 to 17 days. Table 2 cites seven of these patients.

Tonometric readings before and after oxyphenonium revealed no significant alteration in intraocular pressure. However, there is no doubt that oxyphenonium may precipitate glaucoma, as may any mydriatic.

The cycloplegia and mydriasis of 5% oxyphenonium are so intense that they cannot be counteracted individually with 2% pilocarpine, 0.5% physostigmine, 1.5% carbochol, or 0.1% diisopropyl fluorophosphate, or by the cumulative action of all together. Therefore, oxyphenonium should be used only when there is no danger of precipitating glaucoma.

TABLE 2.—*Cycloplegia*

Age	Race	Onset, Min.	Completed, Min.	Residual Accommodation, D.	Duration, Days
31	W	35	55	+ 1.00	10
25	W	30	58	+ 1.00	10
14	N	35	62	+ 1.00	8
30	W	45	80	+ 0.50	7
30	N	35	55	+ 0.50	7
42	W	30	85	+ 0.75	7
29	N	35	90	+ 1.50	17
Average	..	30-45	55-90	+ 0.50-+ 1.50	7-17

TABLE 3.—*Comparison of Oxyphenonium and Atropine*

Age	Race	Drug	Mydriasis		Cycloplegia		Duration, Days	
			Onset *	Completed *	Onset *	Completed *	Mydriasis	Cycloplegia
5	N	Oxy.	20	50	20	45	20	16
		Atr.	20	35	20	35	12	12
6	W	Oxy.	15	45	25	66	20	10
		Atr.	20	45	20	45	14	9
7	N	Oxy.	30	40	30	49	15	14
		Atr.	30	40	30	40	11	8
4	W	Oxy.	15	37	27	40	17	14
		Atr.	20	40	20	40	11	9
11	N	Oxy.	20	40	20	40	17	10
		Atr.	20	40	20	40	11	10
5	N	Oxy.	35	55	20	45	20	16
		Atr.	35	55	20	40	12	10
4	N	Oxy.	25	55	25	55	16	12
		Atr.	25	55	25	55	12	11

* Time expressed in minutes.

The comparative cycloplegic and mydriatic effects of 1% atropine and 5% oxyphenonium bromide were studied in seven children with normal eyes. One drop of atropine was instilled in the right eye and one drop of oxyphenonium was instilled in the left eye of each child.

Table 3 illustrates that oxphenonium mydriasis was slightly more rapid in onset and was completed in the same time as atropine. Oxyphenonium mydriasis began in 15 to 35 minutes, whereas with atropine it commenced in 20 to 30 minutes. The completion time ranged from 35 to 55 minutes for both drugs. Mydriasis with oxyphenonium lasted 15 to 20 days; with atropine, 11 to 14 days. The mydriasis was maximal with both drugs.

In these seven children, oxyphenonium cycloplegia commenced in 20 to 30 minutes and was complete within 40 to 66 minutes. Atropine cycloplegia began

in approximately the same time but was completed sooner. The duration of the cycloplegia was greater in the oxyphenonium-treated eyes, lasting 10 to 18 days, as compared with 8 to 12 days with atropinization.

ALLERGIC REACTIVITY

Six patients with ocular pathology, requiring mydriasis, developed allergic sensitivity while under treatment with atropine. Varying degrees of allergic dermatitis, conjunctivitis, and urticaria were manifested. Postoperative cataracts, congenital cataract, iritis, and uveitis were included in this group. One child, during atropinization for refraction, developed fever and an erythema. Oxyphenonium substituted in these cases and continued for three to eight weeks resulted in a cure of the allergies without untoward reactions.

Oxyphenonium was used routinely in more than 100 cases of ocular inflammatory, traumatic, and postoperative conditions, requiring mydriasis or cycloplegia. Oxyphenonium drops were used once to six times daily without complaint except for a burning sensation. In four cases the burning was sufficiently severe to indicate terminating the use of the drug. In one case, oxyphenonium was used for four months without ill effect.

This treated group included preoperative and postoperative cataract patients and patients with traumatic cataracts, iridencleisis, postoperative retinal detachments, corneal transplantations, corneoscleral lacerations, iridocyclitic states, corneal ulcers, optic neuritis, and thrombosis of the central retinal vessels.

COMMENT

One drop of 5% oxyphenonium bromide solution maintained cycloplegia and mydriasis for periods up to two weeks. Of great value is the possible elimination of multiple daily doses of a drug to maintain a wide pupil in irritable and postoperative eyes. The maintenance of mydriasis in such eyes thus becomes a periodic office procedure, with the assurance of a satisfactory result, independent of the patient's cooperation.

Because of the burning sensation caused by oxyphenonium, the drug cannot be used in children as a cycloplegia for refraction.†

SUMMARY AND CONCLUSIONS

Oxyphenonium bromide (Antrenyl) in a 5% ophthalmic buffered solution, is presented as an effective substitute for atropine.

Oxyphenonium is a strong anticholinergic drug, pilocarpine antagonist, and autonomic ganglion-blocking agent.

Its intense cycloplegic and mydriatic action is more prolonged than that of atropine, as demonstrated by use in hundreds of eyes.

Oxyphenonium can be substituted in treatment of patients allergic to atropine, since no allergic reaction to oxyphenonium has been noted.

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† Continued investigation of 5% oxyphenonium in an ointment base has resulted in elimination of the burning sensation, thus making possible a wider use of the drug.

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FACTORS INVOLVED IN SEVERAL TESTS OF BINOCULAR DEPTH PERCEPTION

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SEVERAL previous investigations * have compared tests purporting to measure the efficiency of binocular depth perception and have attempted by statistical procedures, i.e., by techniques of correlation and, in some cases, by factor analysis, to determine the extent to which the scores agree with one another in measuring individual differences in the efficiency of depth perception. In general these studies have shown poor agreement in the measures provided by different tests, especially when subjects with subnormal visual acuity were excluded.

From a consideration of the many factors involved in the visual discrimination of differences in distance, it appears that this function is a complex one and that various tests might therefore all be valid measures of somewhat different aspects of depth perception. In the present study, several representative tests have been investigated from an analytical rather than from a statistical point of view in order to determine what particular aspects of depth perception each one is best fitted to measure.

THEORETICAL CONSIDERATIONS

A. Distinction Between Binocular and Monocular Perception of Depth.—In considering the group of factors related to ability to detect differences in distance, a distinction can be made between the clues which are operative only in binocular vision and the uniocular clues, which can function both in monocular and in binocular vision. There are several reasons why more attention has been paid to the development of tests dependent upon the binocular rather than upon the uniocular clues.

Many of the uniocular clues, such as the overlapping of contours,† the distribution of light and shadow, and the complex of clues which come under the general category of perspective factors, cannot easily be varied in a quantitative manner for experimental study. The uniocular clue based upon the visual angles subtended by the test objects may provide no real information if the observer does not know their actual sizes. In certain situations, for example, when the two objects whose distances are compared are known to be the same size, the regular change in subtense with distance provides a quantitative clue whose efficiency can be measured.

From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital.

This study was carried out under Contract NONR-248(24) between The Johns Hopkins University and the Office of Naval Research.

* References 1 to 6.

† References 7 and 8.

The accommodation clue, determined by changes in the divergence of the rays of light with distance, is also amenable to quantitative study. Motion parallax, based on a difference in the rate of movement of the retinal images across the retina with lateral movement of the observer's head relative to the test objects, is another aspect which can be varied and studied quantitatively.‡ One important reason why more tests have not been developed for measuring differences in sensitivity to the various uniocular clues is that these perhaps depend less upon physiological factors pertaining to the eyes than upon past experience and training. Probably the most valid reason for the greater attention paid to binocular than to monocular depth perception is the fact that under many conditions binocular vision provides a much greater sensitivity to differences in depth than does monocular vision.

B. Factors in Binocular Depth Perception.—There is some difference of opinion as to the number of clues to depth perception contributed by binocular vision. Some authors list as independent clues horizontal retinal disparity, physiological diplopia, and changes in convergence. A distinction may be made between the clues of retinal disparity and those of physiological diplopia if the former term is applied only to disparities too small to produce diplopia. The simultaneous stimulation of horizontally disparate retinal elements within Panum's area can result in fusion and in the immediate perception of a difference in depth. When, on the other hand, the disparities are such that the retinal elements stimulated lie outside Panum's areas, they can result in physiological diplopia.

A distinction can also be made between the clue determined directly by the physiological diplopia and that based on the changes in convergence normally initiated by this diplopia. If binocular fixation on a given object is maintained, uncrossed double images of a nearer object may be seen, and crossed double images of a more distant object. Ogle [12] has shown that if the separation of the images does not exceed certain limits, physiological diplopia itself provides some ability to discriminate differences in distance. Under the usual conditions of ordinary life, however, when attention is directed to the object seen in double images, convergence is changed until these merge into a single image. On the basis of experiments comparing the stereoscopic acuity with and that without change of convergence, Wright [13] concluded that convergence makes a significant contribution, which becomes steadily greater with increase in the lateral separation of the objects compared. The binocular convergence clue probably depends upon the fact that the retinal images of objects at different distances move across the two retinas in opposite directions, or, if in the same direction, by different amounts. It is, therefore, very similar to the monocular clue based on motion parallax.

C. Tests for the Efficiency of Binocular Depth Perception.—The three forms of tests investigated in the present study (later to be described in detail) are the Howard-Dolman test, the Verhoeff Stereopter, and a depth perception test developed by this laboratory for the Armed Forces Vision Tester. The last [14] is commonly described as a stereoscopic test because separate test targets are presented to each eye by means of a lens-prism stereoscope. In all three forms of test clues associated with binocular vision are of primary importance. Significant differences in the experimental conditions can, nevertheless, be present in such tests; these may result

‡ References 9 through 11.

in differences not only in the absolute values of the threshold parallactic angle but also in the relative rankings of individual subjects as to their sensitivity to differences in depth. The results of our experiments can best be understood if these factors are first discussed in some detail in relation to the three types of tests investigated.

1. Auxiliary Uniocular Clues: (*a*) Moving rod test. In the most commonly used version of the Howard-Dolman test, the subject's task is to set a movable rod so that it appears to be at the same distance as a fixed rod located at a distance of 6 meters from the eyes. With variation in the distance of the adjustable rod there are regular changes in the size of the retinal image and in the amount of accommodation required for a clearly focused image. Uniocular size and accommodation clues may therefore be available, in addition to the binocular clues. Since the subject knows that the two rods are equal in diameter, a perceptible difference in size of the retinal

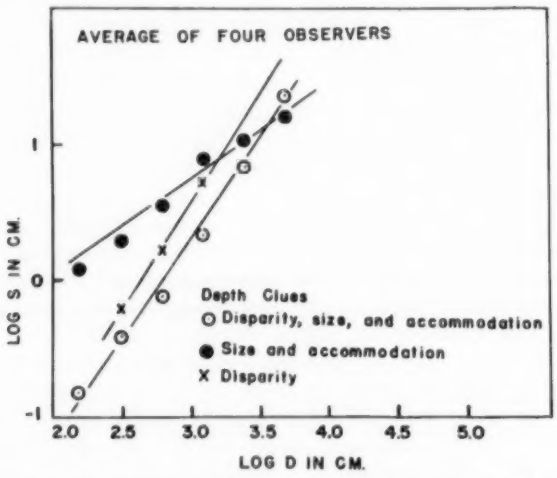

Fig. 1.—Change in MV (mean variation) scores with distance when different binocular and uniocular clues are available. The data, taken from a study by Holway and associates,[17] represent the average thresholds of four subjects.

images can give unequivocal information as to the difference in distance. The relative sensitivity to uniocular and to binocular clues in the conventional Howard-Dolman test has been investigated by Deyo.[15] She found that the average monocular threshold (based on the average-error score) of 100 subjects was 6.35 times the average binocular threshold. Hirsch and Weymouth [16] obtained ratios of the monocular to the binocular threshold of 2.81, 2.04, and 1.77 for testing distances of 61, 122, and 183 meters, respectively. Recent studies by Holway and associates,[17] at distances ranging from 1.5 to 48 meters, also show an inferiority of monocular to binocular depth perception and a gradual decrease in the ratio of the monocular to the binocular threshold with increasing distance. At 6 meters, the distance commonly employed in the Howard-Dolman test, the average monocular threshold (mean variation of equality settings) of their four observers was about five times the binocular threshold.

Prior to the studies of Holway and his co-workers, findings of this sort have generally been interpreted to mean that for the subject with a normally functioning mechanism of binocular vision the retinal disparity clue is the sole determiner of the depth threshold in the Howard-Dolman test. Holway and co-workers, on the other hand, believe that the sensitivities to the clues of retinal disparity, size, and accommodation are additive and that, even though the thresholds of the uniocular clues are greater, they may, nevertheless, supplement the binocular disparity clue. This conclusion is based on their experiments showing that the binocular thresholds were higher when there were no concomitant changes in size and in accommodation associated with changes in retinal disparity. Figure 1, based on data derived from Table XXXI of their study, illustrates some of the findings. In the graph, the distance, D, of the fixed test object is shown on the abscissa; S, the mean variation in the equality settings, on the ordinate. Both are plotted in logarithmic units. The values of S are the averages for four observers, each of whom made 50 determinations at each distance. The data indicated by solid circles and by clear circles show, respectively, the thresholds for monocular vision, in which only size and accommodation clues were available, and the thresholds for binocular vision, in which the disparity clues were also present. It can be seen from the graph that the monocular threshold increased with distance more slowly than the binocular, so that the two thresholds became equal at a distance of about 40 meters. Hirsch and Weymouth,[16] on the other hand, found that the monocular threshold was higher than the binocular even at a distance of 183 meters. The relatively greater sensitivity to the uniocular clues revealed in Holway's study can be attributed to a difference in the experimental conditions. In Hirsch and Weymouth's studies the two rods whose distances were compared were separated laterally; in Holway's tests they were in vertical alignment. The latter condition would be expected to provide a higher sensitivity to the uniocular clues of changes in subtense and in divergence of the rays.

In Figure 1, the data indicated by crosses show the average depth thresholds of Holway's four observers when retinal disparity was the only variable. These measurements were obtained by presenting the same vertically aligned test targets in a mirror haploscope. It is apparent from the graph that the binocular thresholds were significantly higher when the disparity clues were not supplemented by the uniocular clues of size and accommodation. At a testing distance of 6 meters, for example, the threshold was about twice as great (difference of 0.32 in log units) when size and accommodation were held constant. Inspection of the data giving the thresholds of each of the four observers suggests that individual subjects may differ as to the increases in threshold which occur when there are no corresponding changes in subtense and in accommodation associated with the changes in retinal disparity. This is illustrated in the data for Subjects Z and J in Figure 2. The increase in log threshold at 6 meters with removal of the uniocular clues was about 0.25 for Subject W and about 0.75 for Subject J. Comparison of J's monocular thresholds with those of the other three subjects suggests that he has an unusually high sensitivity to the uniocular clues.

Since a change in distance from 6 to 5 meters produces a change in vergence of only about 0.05 D., it is unlikely that accommodation clues could be of significance in the Howard-Dolman test. The contribution of size clues is, moreover, probably

not as great as that observed in Holway's studies because of the lateral separation of the rods of the conventional Howard-Dolman test. The presence of size clues may, nevertheless, be a possible source of disagreement in the findings on this test when compared with tests in which the uniocular size clues are not in accord with the disparity clue.

(*b*) Stereoscopic test. The depth perception test of the Armed Forces Vision Tester is a stereoscopic test in which the separate targets for the right and left eye are viewed in a lens-prism stereoscope. The apparent depth depends, therefore, solely upon retinal disparity. There are in the literature many references to the fact that the threshold parallactic angle measured by such tests may be greater than that determined by other methods. Langlands,[18] for example, reported comparative measurements of the parallactic angles determined with Pulfrich's stereoscopic plates

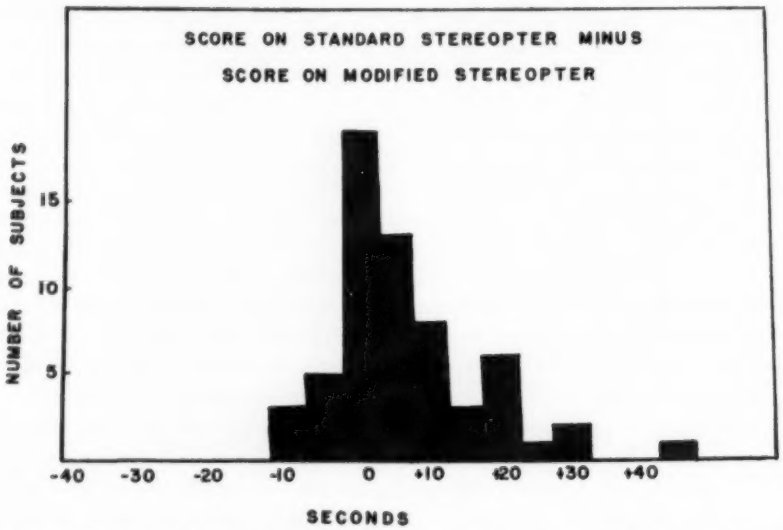

Fig. 2.—Change in MV scores with distance for two of Holway's four subjects. The symbols have the same meanings as in Figure 1.

and with a two-rod test in which the thresholds were determined by the method of constant stimuli. On the stereoscopic test the thresholds of the 10 subjects ranged from 25 to 60 seconds; on the two-rod test, 1.8 to 17 seconds. Wölfflin [19] called attention to the fact that perception of depth in a stereoscope develops slowly for some subjects. Hamburger [20] stated that in a group of subjects all of whom had good and equal acuity in the two eyes, from 10 to 20% could not learn to operate a stereoscopic range finder because they had thresholds 10 or more times those of good operators. Hirsch [21] believes that the scores on stereoscopic tests, as administered at present, are influenced by some factor other than retinal disparity "to such an extent that the individual differences in distance discrimination are obscured."

If there are any factors in the experimental situation which lead the subject to believe that the test targets are all at the same distance, this information may act in opposition to the information provided by the retinal disparities. In instruments

such as the Ortho-Rater, the Sight Screener, the Tele-Binocular, and the Armed Forces Vision Tester, the tests of phoria and of visual acuity which precede the test of depth perception accustom the subject to expect to see a series of test targets all of which lie in the same plane. The studies of Holway and associates suggest that the absence of concomitant changes in size of the retinal image and in the accommodation required for clear imagery might decrease the sensitivity to differences in depth measured on stereoscopic tests. This conflict in the information provided by uniocular and by binocular clues should be of greatest significance when large differences in depth are simulated by retinal disparity. If the simulated differences in depth are small, the changes in size of the retinal image and in accommodation normally associated with them may be well below the threshold. In the Vision Tester, for example, the largest angular disparity presented in the test series, namely, about 40 seconds, corresponds to test objects at simulated distances of 800 and 871 cm. With this difference in distance, there is normally a difference in size of the retinal images of about 2% and a difference in accommodation of about 0.003 D. The latter is certainly well below the threshold. A difference of 2% in size of retinal image can, however, be perceived under favorable circumstances.§ It is possible, therefore, that the absence of concomitant size changes associated with the differences in disparity might, in the Vision Tester and in the other such tests, introduce false clues interfering with the perception of the simulated differences in depth. The possibility of eliminating the influence of conflicting uniocular and binocular clues in the stereoscopic tests of depth perception by giving preliminary training in perceiving the simulated depth of stereoscopic devices has heretofore not been adequately investigated. In the Vision Tester, a model is used to demonstrate what the subject may expect to see in the actual test. The preliminary demonstration should aid in overcoming any "mental set" which might result from prior testing with targets all of which are in the same plane. The device consists of a transparent plastic plate with four black circular targets painted on the rear surface and one on the front, to simulate one row of the test targets. As a further aid in the perception of the simulated differences in depth associated with retinal disparity, the targets viewed in the instrument itself include items for preliminary practice, in addition to those comprising the testing series.

(*c*) Verhoeff Stereopter. In the standard form of this test one of the three rods is either nearer or more distant than the other two by a fixed distance of 2.5 mm. The rods differ in width (2, 2.5, and 3 mm.) and are so oriented that in each of the eight arrangements the size clues are opposed to clues from retinal disparity and from accommodation. It should be emphasized, however, that rods of equal diameter would have to be widely separated to produce the same differences in angular subtense. It may be assumed, moreover, that the observer knows that the rods differ in width even if this is not specifically mentioned in the instructions. It is, therefore, difficult to predict on theoretical grounds alone what effects, if any, result from the introduction of false size clues in this test.

A study by Niven and associates [23] gives experimental data from which it is possible to determine the actual influence of the false size clues on the incorrect responses. Of the five possible incorrect answers, only two can be attributed to the size clues, namely, selection of the largest rod as nearer than the other two, and

§ References 17 and 22.

selection of the smallest as more distant. From Table V of Niven's paper, it can be determined that of the 4,800 responses given by 100 subjects, 563 were incorrect, but that only 304 of these were in accord with the difference in size of the rods. Since by chance alone about two-fifths, or 225, of the incorrect answers would fall into this group, it may be concluded that, although the size clues did in some cases determine the nature of the incorrect responses, a majority of incorrect answers were based solely on chance guesses. To what extent the frequency of incorrect responses is increased, and the threshold of depth discrimination therefore raised, by the presence of false size clues cannot be decided from Niven's study.‖

2. Distance of Test Targets: In our studies the Howard-Dolman test was administered at the usual distance of 6 meters. The depth targets of the Armed Forces Vision Tester are at an optical distance of 8 meters; i. e., the accommodation and convergence required for clear imagery and for fusion of the right and left eye targets are the same as those required for objects actually located at 8 meters from the eyes. It has been shown in previous studies of the phoria and acuity components of the Vision Tester ¶ that "apparatus convergence" and "apparatus accommodation," resulting from the subject's awareness of the true distance of the targets, have no significant influence on the measurements of phoria and acuity. These findings do not, however, rule out the possibility that the artificial viewing conditions might interfere with the ability to perceive the simulated differences in depth.

In the Stereopter the distance of the test targets from the subject is varied in order to determine the minimum discriminable angular disparity. According to Jonkers' study,[26] the maximal distances at which correct depth judgments were made ranged from 210 to 90 cm. in 95% of subjects with a normally functioning mechanism of binocular vision. Presbyopes, therefore, even though corrected for distance and for near, are at a disadvantage on the Stereopter when the testing distance falls in the intermediate range not adequately corrected either by the distance or by the near glasses. An uncorrected myopia will reduce acuity for distances of 6 meters or more but will have a less pronounced effect, or none at all, on the acuity for distances of 1 to 2 meters. Subjects with uncorrected myopia may therefore be expected to make relatively higher scores on the Stereopter than on tests of depth perception at distances of 6 meters or more. Differences in testing distance may also lead to discrepant findings in the case of subjects who have difficulty in maintaining the proper convergence if this defect is especially marked either for near or for distant test targets.

Several previous studies have shown that the threshold in angular units is not independent of distance, as might be expected from theoretical considerations. Graham,[27] for example, states that the minimum perceptible angular disparity is smaller at 15 than at 2.5 meters. Hirsch and Weymouth's [16] measurements of the monocular depth thresholds at 61, 122, and 183 meters also show that the threshold, expressed in angular units, decreases with distance. It can be determined from their average data for four observers that the threshold in linear units, S, is approximately proportional to $D^{1.6}$, where D is the testing distance. For a constant angular

‖ The evidence from our own investigations, presented in a later section of this paper, indicates that the thresholds of some subjects are slightly lower when rods of equal width are substituted for the unequal rods of the standard test.

¶ References 24 and 25.

threshold, independent of distance, the linear threshold (S) should be proportional to D^2. The smaller exponent actually observed shows that the angular threshold must decrease with increasing distance. Holway's measurements [17] for six distances, between 1.5 and 48 meters, show a similar effect of distance. In our Figure 1, based on their data, the thresholds determined when disparity, size, and accommodation clues were present, fit the equation $\log S = 1.5 \log D + c$; i. e., S is proportional to $D^{1.5}$.

3. Influence of Aniseikonic Errors: (*a*) Moving rod test. A difference in the horizontal dimensions of the retinal images of the two eyes, because of the retinal disparity it introduces, may influence the apparent depth differences of laterally separated test targets. In the moving rod tests this results in a shift in the position of subjective equidistance, and therefore a constant error in the setting of the adjustable rod. It was shown in a previous study [28] that the opposing perspective clues present in the conventional Howard-Dolman test reduce, but do not entirely eliminate, the constant error associated with horizontal aniseikonia.# It has therefore been suggested in previous studies* that in order to measure sensitivity to differences in depth, as distinguished from constant errors in localization, a variability score should be substituted for the average error score commonly used with the Howard-Dolman test.†

(*b*) Verhoeff Stereopter. A horizontal aniseikonia may produce an apparent rotation of the face of the Stereopter about a vertical axis. This, however, can have relatively little effect on the ability to discriminate the difference in depth of the three rods, because the face of the instrument and the rods themselves provide a plane of reference.

(*c*) Stereoscopic test. In the depth perception test of the Vision Tester, a horizontal aniseikonia may likewise produce an apparent rotation of the plane of the test targets, but this does not interfere with correct judgments as to which one of the five targets is nearer than the other four.[31]

4. Other Differences in Experimental Conditions: Brief mention should be made of other differences in the three forms of tests which might influence either the absolute magnitudes of the depth thresholds measured by each or the relative rankings of individual subjects on each test. With the Stereopter and the Vision Tester, graded fixed intervals of depth are used to determine the smallest difference in depth which can be detected in a certain percentage of trials. The magnitude of the threshold will, of course, depend upon the precentage selected. In the moving rod form of test the score is based on the errors in the settings of equidistance. The differences in the psychophysical procedure used to measure the threshold may be expected to lead to differences in its absolute magnitude. Differences in the dimensions and lateral separations of the test targets and in the luminances of the background may likewise influence the thresholds. These variable factors would,

* References 28 and 30.

If vertically aligned test targets are substituted for the laterally separate ones, constant errors may still occur, attributable in this case to cyclophorias, declination errors, etc.[29]

† Whether or not the constant-error score should also be considered depends upon the circumstances. In the selection of men to operate stereoscopic range finders, for example, a high constant error is probably of no significance, provided the sensitivity to differences in depth is adequate.

however, not necessarily reduce the correlation between the test scores. The fact that the moving rod type of test requires eye-hand coordination on the part of the subject might, on the other hand, reduce its correlation with tests in which fixed differences in depth are presented.

EXPERIMENTAL INVESTIGATIONS

A. Instruments and Procedure.—In our studies the experimental conditions under which the three tests were given were chosen to eliminate as far as possible differences which are not essential elements of each test.

1. Howard-Dolman Test: In the administration of this test a chin rest was used to prevent lateral movements of the subject's head. The subject adjusted the position of the movable rod by turning a wheel instead of by pulling alternately on one of two cords. This modification was introduced in order to minimize the factor of motor skill. The test procedure has been described in detail in an earlier study.[28] For reasons already discussed, a variability score was used to measure sensitivity

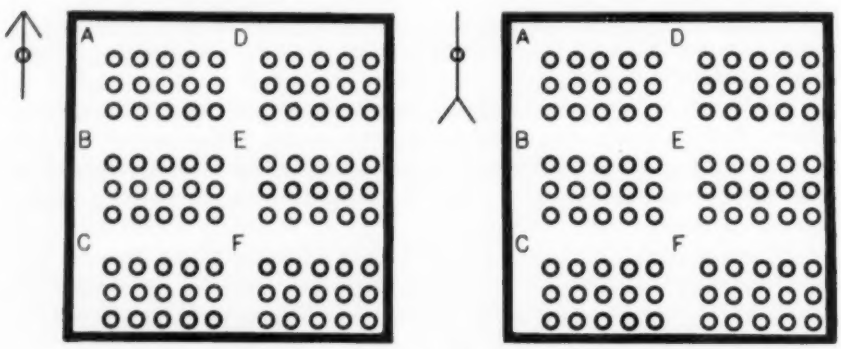

Fig. 3.—Depth perception targets of the Armed Forces Vision Tester.

to differences in depth. The mean variation, rather than the standard deviation, was chosen as the measure of variability because of the following practical considerations: The former is much simpler to compute, and for the majority of subjects showing no appreciable constant error it does not differ significantly from the average-error commonly used. The results of a preliminary study reported in the next section suggest, moreover, that when each subject makes only 10 settings of the movable rod, the mean variation and the standard deviation give essentially the same estimates of individual differences in depth perception.

2. Depth Perception Test of the Armed Forces Vision Tester: Figure 3 shows the test targets presented to each eye. The incomplete arrows at the left of each target provide a preliminary check of the subject's binocular vision. Lateral separation of the right and left components of the arrow is an indication of esotropia or exotropia. Vertical separation, so that two circles are seen one above the other on the shaft of the arrow, is an indication of hypertropia. Failure to see either the head or the tail of the arrow indicates suppression of the image received on one fovea. If the subject shows evidence of a tropia, or of continuous or intermittent suppression of the foveal image of one eye, on this preliminary test, it may be

assumed that he cannot perceive the simulated differences in depth of the circle targets. The arrow target may therefore be used as a quick means of eliminating such subjects without further testing.

The procedure used to measure the threshold of binocular depth perception followed exactly that outlined in the "Manual of Instructions,"[14] which reads as follows:

> The depth slide used to test depth perception consists of a number of horizontal rows of circles, five circles in each row, one of which should appear slightly nearer to the examinee than the other four. In order to explain the test, the examinee is first shown a demonstration device consisting of a transparent plastic plate with four black circles on the rear surface, one on the front. As in the depth perception test itself, therefore, one circle appears nearer than the other four. After the plastic model of the test has been shown, the examinee is told to look into the instrument and his attention is directed to Group A, the three rows of circles in the upper left hand corner of the square. This first group is to be used to further explain the test and allow time for the perception of depth to develop. The top row of five circles in Group A demonstrates a relatively large difference in depth, the middle row a moderate difference, the bottom row a small difference. Some examinees may not see any depth for the first minute or so, and in such cases the examiner must not hurry through the practice test. He may tell the examinee the correct answers for the three rows of Group A and instruct him to look at each circle in turn until he can see that one of the five circles in each row is nearer to him than the others. The examiner may use the occluder to demonstrate that with monocular (one-eyed) vision all the circles appear in the same plane, while with binocular (two-eyed) vision one may appear nearer than the other four. When the examiner is satisfied that the examinee actually sees depth in at least the top row, he may proceed to the actual test. *This is given without any help or hints from the examiner such as are used in the practice period.* The examinee is asked to indicate by number, counting from left to right, which circle is nearer in the top, the middle, and the bottom row of Group B. If all three answers are correct, the same questions are asked for Group C, Group D, etc. The test is discontinued when the examinee gives one or more incorrect answers in any one group beyond Group B. (If one or more incorrect answers are given in Group B, the examiner repeats the practice session with Group A, then has the examinee try Group B again, followed by Group C, etc., if correct answers are now given in Group B.) The score is the letter of the last group in which no errors are made. If the first test group, i. e., Group B, is failed a second time, the score is recorded as 0.

3. Verhoeff Stereopter: The equipment used for this test differs in several respects from the instrument manufactured by the American Optical Company. A chin rest was used to maintain a fixed position of the subject's head. The instrument was not held in the hand but was supported in a mount so that its face would always be in the frontoparallel plane. Its distance from the subject was read from a centimeter scale. The illumination was supplied by a 6-volt flashlight bulb operated on alternating current from a transformer. Prior to the actual tests, the subject was allowed to examine the targets at close range, where it was demonstrated that one of the three rods was always either in front of or behind the plane of the other two. The testing procedure was essentially the same as that employed by Niven and associates,[23] in that the subject was required to designate one of the three rods as either nearer or more distant than the other two. The standard instructions on the other hand, follow Verhoeff's recommendations[22] and permit the subject to select one rod as nearest and another as farthest. We found, however, that because the subject had already been told that two of the three rods were always at the same distance, these contradictory instructions were confusing. The test consisted in presentations of the test targets at different distances, in order to determine the greatest distance at which seven of eight responses were correct. The series of fixed

distances employed, and the corresponding parallactic angles, are listed in Table 2. The angular values were computed from the formula $A = 33/D^2$, in which D is the distance, in meters, and A the parallactic angle, in seconds. This formula assumes an interpupillary distance of 64 mm.

B. Results.—1. Comparison of Mean Variation and Standard Deviation Scores on the Howard-Dolman Test: From the data provided by 10 adjustments of the movable rod, the mean variation and the standard deviation of the settings were computed. Table 1 is a frequency table showing for 100 subjects the relationship between the two variability scores. Because of the close agreement, obvious to inspection, the simpler mean variation scores were used in later studies in which the Howard-Dolman scores were compared with those of other tests.

2. Effect of False Size Clues of the Verhoeff Stereopter: In order to determine whether the false size clues of the Verhoeff Stereopter have any significant influence on the test scores, 68 subjects were tested with the standard Stereopter and with

TABLE 1.—*Relationship Between Two Measures of Variability on the Howard-Dolman Test*

Mean Variation, Mm.	Standard Deviation, Mm.										
	0.0-9.9	10.0-19.9	20.0-29.9	30.0-39.9	40.0-49.9	50.0-59.9	60.0-69.9	70.0-79.9	80.0-89.9	90.0-99.9	100 or Greater	
100 or greater	..	..	..	..	..	..	..	..	..	..	1	1
90.0-99.9	..	..	..	..	..	..	..	..	..	..	2	2
80.0-89.9	..	..	..	..	..	..	..	..	..	..	..	0
70.0-79.9	..	..	..	..	..	..	..	..	1	..	..	1
60.0-69.9	..	..	..	..	..	..	1	4	1	..	..	6
50.0-59.9	..	..	..	..	..	1	1	2	..	1	..	5
40.0-49.9	..	..	..	..	1	8	3	..	..	..	..	12
30.0-39.9	..	..	..	3	2	2	..	..	..	..	..	7
20.0-29.9	..	..	6	14	1	..	..	..	..	..	..	21
10.0-19.9	..	21	13	..	..	..	..	..	..	..	..	34
0.0-9.9	4	7	..	..	..	..	..	..	..	..	..	11
	4	28	19	17	4	11	5	6	2	1	3	100

a modified instrument in which rods 2 mm. in width were substituted for the 3, 2.5, and 2 mm. rods of the standard device. Three separate measures of the threshold distance were made, i. e., with (1) equal, (2) unequal, and (3) equal rods, or with (1) unequal, (2) equal, and (3) unequal rods. The first test was considered as a practice series, and comparisons were based solely on the results of the second and third tests. In each group of determinations the subject knew whether the rods would be equal or unequal in width. The order of testing was alternated so that one-half of the group started with rods of equal width, the other half with rods of unequal width.

Table 2 shows the relationship between the thresholds determined with and those determined without false size clues. The Pearson product-moment correlation between the two sets of scores is 0.90. It is apparent to inspection that the thresholds tend to be slightly greater with unequal than with equal rods. The magnitude of the increase in threshold associated with the false size clue is better shown in Table 3, which gives for 61 subjects the distribution of the difference in the thresholds. The data for seven subjects whose thresholds were greater than 90 seconds in one or both tests are not included. For these subjects the differences might be

spuriously great because tests were not made at intermediate distances between 50 cm. (132 seconds) and 60.3 cm. (90 seconds). For 48 of the 61 subjects the thresholds determined by the two methods agreed within ± 10 seconds. For the other 13 the thresholds were from 15 to 45 seconds greater when false size clues were present.

There are several possible interpretations of these findings. According to Verhoeff,[32] the small group of subjects who are influenced by the false size clues should be considered as having inferior depth perception, because only disparity

TABLE 2.—*Relationship Between Scores on Standard and on Modified Stereopter*

Modified		Standard, Sec.													
Cm.	Sec.	10	15	20	25	30	35	40	45	50	60	70	80	90	132
50.0	132	..	..	..	..	..	..	..	..	..	..	..	..	1	**2**	3
60.5	90	..	..	..	..	..	..	..	..	..	..	..	..	..	2	2
64.1	80	..	..	..	..	..	..	..	..	..	..	1	..	..	2	3
68.5	70	..	..	..	..	..	..	..	..	..	1	..	1	2	..	4
74.2	60	..	..	..	..	..	..	..	..	..	1	..	..	1	..	2
81.0	50	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0
86.0	45	..	..	..	..	..	..	..	2	1	1	1	..	..	..	5
91.0	40	..	..	..	..	1	..	..	..	..	1	1	..	..	..	3
97.0	35	..	..	..	..	..	2	2	1	..	..	..	1	..	..	6
105.0	30	..	..	..	1	1	2	..	..	1	..	..	..	..	..	5
115.0	25	..	..	2	3	2	2	1	..	..	..	..	..	..	..	10
128.0	20	..	2	2	3	2	1	2	..	..	..	..	..	..	..	12
148.0	15	..	4	1	2	..	..	..	..	..	..	..	..	..	..	7
181.0	10	4	2	..	..	..	..	..	..	..	..	..	..	..	..	6
		4	8	5	9	6	7	5	3	2	4	3	2	4	6	68

TABLE 3.—*Distribution of Differences in Scores on Standard and on Modified Stereopter*

Score on Modified Test Minus Score on Standard Test, Sec.	No. of Subjects
−10	3
− 5	5
0	19
5	13
10	8
15	3
20	6
25	1
30	2
35	0
40	0
45	1
Total	61

clues can be relied upon always to give the correct information. There is, on the other hand, evidence suggesting that auxiliary monocular clues normally supplement and increase the efficiency of binocular depth perception (Holway [17]; Vernon [33]), and that sensitivity to monocular, as well as to binocular, clues is therefore a desirable condition. From this point of view, tests in which monocular and binocular clues are in opposition may give misleading information. In this connection, it should be pointed out that the data of Table 2 show that on the Stereopter a significant increase in the threshold with opposing size clues is not limited to subjects with relatively poor depth perception. This suggests that the relative importance

of uniocular and binocular clues may be an individual trait, not necessarily related to the efficiency of binocular depth perception. On theoretical grounds, therefore, it is possible that the elimination of the opposing size clues in the Verhoeff test might give a more valid test of binocular depth perception. In view of the high correlation of the test scores obtained with and without the false size clue, however, it is probable that its presence or absence will not appreciably influence the agreement between the Stereopter and other tests of depth perception.

3. Comparison of Three Tests of Depth Perception: This section presents data for subjects given two or more different tests of depth perception in order to investigate the extent of the agreement in the results of different tests. The subjects used for the various comparisons were in many instances the same persons.

All had visual acuities of at least 20/40 in each eye. It is well recognized that acuity is a limiting factor in any form of depth test based on horizontal retinal disparities. For maximal correlation between acuity and depth scores, vernier acuity for the discrimination of vertical contours should be measured. Acuities

TABLE 4.—*Relationship Between Scores on Howard-Dolman Test and on Modified Steretopter*

Verhoeff, Parallactic Angle, Sec.	Howard-Dolman, Mean Variation, Mm.										
	10 or Less	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51 or Greater	
15 or less	3	1	1	1	..	..	..	..	..	..	6
20-25	5	2	2	..	..	..	..	..	..	..	9
30-35	..	5	0	1	..	..	..	..	..	1	7
40-45	1	1	2	1	1	..	..	1	..	..	7
50-55	..	..	..	..	..	..	..	..	..	..	..
60-65	..	..	..	..	..	..	..	..	..	..	..
70-75	..	..	..	..	..	1	..	..	..	..	1
80-85	..	..	..	..	..	..	..	..	1	..	1
90 or greater	..	..	..	1	..	..	1	1	2	1	6
	9	9	5	4	1	1	1	2	3	2	37

measured with the conventional letter targets would not be expected to correlate as well with depth perception, because blurring of the retinal image in any meridian impairs acuity for such targets, whereas blurring only of vertical contours impairs depth perception. Subjects whose acuity for letter targets is less than 20/40 will, however, usually have poor depth perception. Practical considerations suggest therefore that, in the selection of subjects for tasks requiring good depth perception, those with a visual acuity less than 20/40 in either eye can be automatically excluded without further testing.

(*a*) Howard-Dolman test and modified Stereopter test. Table 4 shows, for 37 subjects, the relationship between the mean variation (MV) scores, in millimeters, on the Howard-Dolman test and the threshold parallactic angles, in seconds, measured on a modified Stereopter in which the three rods were equal in width. It may be seen from the Table that 27 of the 28 subjects with MV scores of 30 mm. or less on the Howard-Dolman test had scores of 45 seconds or better on the Stereopter. Of the nine subjects with MV scores greater than 30 mm. on the former test, seven had thresholds greater than 45 seconds on the latter. The one subject who made a score of 25 mm. on the Howard-Dolman test but was unable to distinguish differences in depth on the Stereopter at 50 cm. (132 seconds) made

a zero score on the Vision Tester and on the preliminary fusion test showed evidence of intermittent suppression of the retinal image of one eye. This intermittent loss of binocular vision could account for the poor scores on the Stereopter and the Vision Tester, since at each level of difficulty correct responses must be given to seven of eight items on the former test and to all three items of the latter. In the Howard-Dolman test, on the other hand, short intervals in which binocular vision was lost would not necessarily result in a significant increase in the mean variation score computed from 10 independent settings. One of the two subjects with a very poor score on the Howard-Dolman test and a good score on the Stereopter had an uncorrected myopia of 0.25 D. in the right eye and 0.50 D. in the left eye. His acuity at 6 meters was 20/20, right, and 20/25, left. The uncorrected myopia may account for this subject's poorer score on the Howard-Dolman test than on the Stereopter. In the second case there was no obvious explanation for the relatively poorer performance on the Howard-Dolman test.

TABLE 5.—*Relationship Between Depth Scores on Howard-Dolman Test and on Standard Stereopter*

Verhoeff, Parallactic Angle, Sec.	Howard-Dolman, Mean Variation, Mm.										
	5-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51 or Greater	
15 or less	2	..	..	1	..	..	..	..	..	..	3
20-25	6	3	1	1	..	..	..	..	..	..	11
30-35	..	3	3	..	..	..	..	..	..	..	6
40-45	..	2	2	..	..	..	..	..	..	..	4
50-55	..	..	..	..	..	..	..	1	..	1	2
60-65	1	..	..	..	1	1	..	..	..	..	3
70-75	..	..	..	1	..	..	..	..	..	..	1
80-85	..	..	..	..	..	..	..	..	..	..	..
90 or greater	..	..	..	1	..	..	..	..	1	1	3
	9	8	6	4	1	1	..	1	1	2	33

With these three exceptions, critical scores of 30 mm. on the Howard-Dolman test and 45 seconds on the modified Stereopter test agree in their classification of subjects on a pass-fail basis. The data suggest, however, that within the group showing good depth perception there is no close agreement in relative ranking on the two tests. This is not surprising, since others [34] have found that the conventional Howard-Dolman test, while adequate to distinguish between "normal" and "subnormal" depth perception, does not differentiate within the "normal" group.

In order to compare the absolute values of the thresholds in angular units, the millimeter scores of the Howard-Dolman test may be converted to seconds of parallactic angle by the formula $A = S/2.7$. (The constant 2.7 in this formula assumes an interpupillary distance of 64 mm.). When this conversion is made, it it apparent that much smaller values of parallactic angle can be discriminated on the Howard-Dolman test than on the Stereopter. A score of 30 mm. on the former, for example, corresponds to an angular disparity of 11 seconds, whereas the equivalent passing score on the Stereopter is about 45 seconds. This difference in the minimum perceptible angular disparities, as measured by the two tests, is probably accounted for primarily by the distance factor previously discussed. If, in accordance with Holway's findings, we assume that S, the linear threshold, is proportional to $D^{1.5}$ rather than to D^2, then a variation of S from 10 to 30 mm. when D is kept

constant at 6 meters (Howard-Dolman test) should correspond to a variation in *D* from 204 to 98 cm. when *S* is kept constant at 2.5 mm. (Stereopter). This prediction of the equivalent ranges of score on the two tests is not very different from that actually observed in the 27 subjects with good depth perception on both tests.

(*b*) Howard-Dolman test and standard Stereopter test. Table 5 shows for 33 subjects the relationship between the Howard-Dolman scores and the scores measured on the standard Stereopter, in which the three rods differ in diameter. Here, too, a passing score of 45 seconds (86 cm.) on the Stereopter gives the best agreement, with a passing MV score of 30 mm. on the Howard-Dolman test. By these criteria, 24 subjects pass both tests, 5 fail both, and 4 pass the Howard-Dolman test but fail the Stereopter test. One of the last group is the subject with intermittent suppression discussed in the previous section. The failure of the other three is perhaps explained by an especial sensitivity to the false size clues of the standard Stereopter, since when tested with rods of equal diameter they made passing scores of 40 to 45 seconds. The data of Table 5 are similar to those of Table 4 in showing

TABLE 6.—*Relationship Between Scores on Howard-Dolman Test and on Vision Tester*

Depth Test of Vision Tester		Howard-Dolman, Mean Variation, Mm.										
Instrument Score	Parallactic Angle, Sec.	5-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51 or Greater	
F	15-17	5	6	1	2	..	..	..	..	..	1	15
E	21-21.5	1	1	1	..	..	..	..	..	..	..	3
D	25-28	2	1	2	2	..	..	..	..	..	..	7
C	30-32	..	..	..	..	..	..	..	..	..	..	0
B	39-41	..	..	..	..	..	..	..	1	..	..	1
0 *	.....	..	2	3	1	2	1	1	1	4	2	17
		8	10	7	5	2	1	1	2	4	3	43

* A score of 0 indicates that test item B was failed in two successive trials.

that, although there is close agreement in the dichotomous classification of good and poor depth perception, the agreement in scores on the two tests does not extend to differences within each group.

(*c*) Howard-Dolman test and Vision Tester. Table 6 shows for 43 subjects the relationship between the MV scores on the Howard-Dolman test and the arbitrary letter scores of the Vision Tester. The range of parallactic angles corresponding to each letter score are also shown in the Table.‡ Twenty-four of the 43 subjects had MV scores of 25 mm. or less associated with Vision Tester scores of D or better; 10 had MV scores of 31 or greater associated with scores of B or poorer. On a two-category pass-fail basis, therefore, the tests agree in 34 of the 43 cases. The poor Howard-Dolman score of one subject, making the maximum score of F on the Vision Tester, can probably be attributed to lack of effort, since on a retest two months later he was able to make a correspondingly good score of 11 mm. on the Howard-Dolman test. Eight subjects with scores of 30 mm. or better on the Howard-Dolman test were unable to perceive any depth difference in the easiest items of the Vision Tester, after the standard preliminary practice. Four of these, with MV scores ranging from 11 to 18 on the Howard-Dolman test, were given

‡ Because of difficulties in reproduction, the angular disparities of the three items in each test group vary slightly.

further practice on the Vision Tester and on other stereoscopic devices. One showed no improvement; the other three made the maximum score of F. Studies of a much larger group are needed to determine what proportion of subjects have especial difficulty in perceiving differences in depth under the artificial conditions present in the Vision Tester. It is also important to find out whether such subjects can eventually learn to operate stereoscopic devices, such as range finders, or whether they will continue to show inferior ability.

(*d*) Factors responsible for consistently poor depth perception on all tests. The subjects whose depth scores are shown in Tables 4, 5, and 6 include a total of 11 with poor depth perception on every test that was given. Additional information pertaining to these subjects suggests possible factors responsible for their subnormal binocular vision. Two showed an intermittent and two a constant suppression of the retinal image of one eye on the preliminary fusion test. In two other subjects a lateral tropia was revealed by this test.§ The other five subjects showed no evidence of either suppression or tropia on the fusion test. Two were later examined in the Orthoptic Clinic of the Wilmer Institute and found to have intermittent tropias at distance. Two others, who wore glasses during the depth tests, had high anisometropic errors of refraction. One of these was tested on the space eikonometer and was found to have an aniseikonic error requiring a correction of 3% axis 180, right eye, and 1% axis 90, left eye. The only explanation found for the poor depth perception of the fifth subject was that the patient was tested while wearing newly acquired glasses. He made a score of 50 cm. (132 seconds) on the Stereopter and an MV score of 49 mm. on the Howard-Dolman test. No measurements were made with the Vision Tester. On retests after the glasses had been worn for three weeks the Stereopter threshold was 91 cm. (40 seconds) and the MV score was 16 mm.

In these 11 subjects, consistently poor depth perception appears to have been associated primarily with obstacles to binocular fusion. Seven of the 11 had visual acuities of 20/20 or better in each eye. In four cases the visual acuities of 20/30 to 20/40 in the poorer eye may have contributed to the poor depth perception. Since phoria tests were not routinely given to this group, the possible effects of heterophoria on their depth perception cannot be evaluated. An additional group, of 109 subjects, was therefore examined on the Vision Tester in order to obtain further information as to the effects of heterophoria and of subnormal acuity on binocular depth perception.

4. Relationship of Acuity and Phoria Scores to Depth Scores on Vision Tester: The 109 subjects were medical students, instructors, secretaries, technicians, clerks, and a few domestic employees of The Johns Hopkins Hospital who volunteered to take the visual tests while awaiting examination in the Personnel Health Clinic of this institution. Appropriate distance tests on the Armed Forces Vision Tester were given for acuity of each eye, vertical and lateral phorias, fusion, and depth perception. About half the subjects scoring less than E on the depth tests were given one or more additional trials, either in the same session or a later date, to see whether their scores improved. Table 7 shows the test and retest scores of the 29 subjects

§ Under the standard conditions recommended for administration of the Vision Tester, failure on the depth test can be assumed, and the test therefore omitted, when an obvious deficiency in binocular vision is revealed by the preliminary fusion test.

given additional trials. It is apparent that there is a considerable learning factor, since 17 of the 29 made higher scores on repetition of the test. The findings suggest that, even though preliminary practice items are provided, poor scores may, nevertheless, result from lack of familiarity with devices in which the uniocular distance clues are not in accord with the binocular disparity clues.

The relationship between the acuity of the poorer eye and the depth score is shown in Tables 8 and 9. Although there was no selection on the basis of visual acuity, only two subjects had acuities less than 20/40. The data indicate that poor

TABLE 7.—*Relationship of Test and Retest Depth Scores on Vision Test*

	First Test				
Retest	0	B	C	D	
0	5	5	..	..	10
B	3	1	..	..	4
C	1	0	1	..	2
D	..	2	3	..	5
E	..	2	2	1	5
F	..	..	1	2	3
	9	10	7	3	29

TABLE 8.—*Relationship Between Acuity of Poorer Eye and First Score on Depth Test*

	> 20/20	20/20	20/25	20/30	20/40	20/50	20/70	
F	19	10	6	1	1	0	0	37
E	5	3	3	0	1	1	0	13
D	5	5	5	1	1	0	0	17
C	4	2	2	2	0	0	1	11
B	5	2	2	1	2	0	0	12
0	2	3	6	3	4	0	0	18
X *	0	0	0	1	0	0	0	1
	40	25	24	9	9	1	1	109

* Failure on depth test assumed because of failure on "arrow test."

TABLE 9.—*Relationship Between Acuity and Depth Scores on Vision Tester*

	Test		Retest (When Given)		
	D or Better	C or Poorer	D or Better	C or Poorer	
20/20 or better	47	18	55	10	65
20/25 or poorer	20	24	22	22	44
	67	42	77	32	109

depth scores occur more frequently in those with acuities less than 20/20 in one or both eyes. Table 9 shows that when the depth scores are based on a single test about 72% of subjects with good acuity have scores of D or better, as contrasted with 46% of those with less than 20/20 in one or both eyes. In the second part of Table 9 the subjects are classified in accordance with the retest depth scores when more than one test was given. In this case the percentages making scores of D or better are 85 in the group with acuities of 20/20 or better and 50 in the group with acuities of less than 20/20 in one or both eyes.

The finding that relatively good depth scores are made by many with acuities ranging from 20/25 to 20/40 is not unexpected, since the effect of blurred imagery

on binocular depth perception varies with the type of uncorrected refractive error. Blurring of the retinal image limited to the vertical meridian (astigmatism at axis 180) reduces acuity but has little effect on the perception of differences in depth based on horizontal retinal disparities. In the small percentage of subjects having relatively poor depth scores associated with acuities of 20/20 or better, factors interfering with binocular fusion could be responsible for the low depth scores. In this group of 109 subjects, the fusion test revealed only 1 case of tropia and none of monocular suppression. Of the seven subjects with measurable amount of hyperphoria, three had 1 to 2 △ of hyperphoria associated with depth scores of D or better and four had hyperphorias of 1 △ and depth scores of C or poorer.

TABLE 10.—*Relation of Lateral Phoria Scores to Depth Scores on Vision Tester*

	First Test		Retest (When Given)		
	D or Better	C or Poorer	D or Better	C or Poorer	
Low phoria (4 exo to 5 eso)	66	33	76	23	99
High phoria (more than 4 exo or 5 eso)	1 *	9 †	1 *	9 †	10
	67	42	77	32	109

* Esophoria of 11 △ or more.
† Eight of these had esophoria scores of 6 to 8 △. One, having an exophoria score of 7 △, was shown by the fusion test to have an exotropia.

TABLE 11.—*Distribution of Depth Scores (Vision Tester) of Subjects Meeting Certain Standards of Acuity, Fusion, and Phoria*

Depth Score	Distribution of Cases According to	
	First Test	Retest *
0	0	3
B	7	0
C	4	0
D	8	9
E	8	12
F	29	32
Total	56	56

* All subjects with scores of C or poorer were retested.

The incidence of hyperphoria is therefore too low for one to determine its possible effect on depth perception.

Lateral phorias of significant amount were also rare in this group, since 99 of the 109 subjects had scores ranging from 4 △ of exophoria to 5 △ of esophoria at distance. In Table 10, showing the relationship of lateral phoria and depth scores, it may be seen that 8 of the 10 subjects with significant lateral phorias had esophoria scores of 6 to 8 △ and depth scores of C or poorer. The one subject having an esophoria greater than 11 △, on the other hand, made a depth of score of D. Since seven of the nine with high phoria scores associated with poor depth scores also had acuities less than 20/20 in one or both eyes, it is possible that their poor depth perception was directly related to low acuity rather than to esophoria.

Our data suggest that when the visual requirements for specific tasks necessitate not only good depth perception but also high acuity and low phoria, many of those with consistently poor depth perception will automatically be disqualified by the

last two tests. Let us suppose, for example, that the qualifying visual standards for a given job category require (*a*) visual acuities of 20/20 or better in each eye, (*b*) absence of tropia or suppression, (*c*) vertical phorias at distance less than 1 △, (*d*) lateral phorias at distance less than 4 △ exophoria or 5 △ esophoria. Sixty of the 109 subjects in our study met the above criteria. If we accept the view that a poor depth score is not significant unless confirmed on repetition of the test, four of those who made depth scores of C or poorer should be omitted because no retests were given. The remaining 56 subjects were all given a retest unless a score of D or better was made on the first test. Table 11 shows for these subjects the distribution of scores based on the first test, for comparison with those based on the retest when one was given. On the first test, 11 made scores of C or poorer; on the retest, only 3. If, therefore, no depth tests were given, the 56 subjects meeting the other visual criteria would include 3, or about 5%, whose depth perception was definitely subnormal. If, on the other hand, only one depth test was given and a score of D or better was required, these three subjects with poor depth perception would be disqualified, as well as eight others who on the basis of the retest scores may actually have good depth perception. Whether or not it is advisable to include a test of depth perception when high standards of acuity, fusion, and muscle balance must also be met depends upon the relative importance of eliminating unsuitable subjects and of not disqualifying suitable ones. In order to have high efficiency in both aspects of selection, poor scores on the depth test of the Vision Tester should be confirmed either by repeating this test or by giving some other form of depth test.

SUMMARY AND CONCLUSIONS

The results of a previous study by Holway and associates indicate that uniocular clues to differences in distance may contribute to binocular depth perception, even though the sensitivity to the uniocular cues, acting alone, is much poorer than the sensitivity to the binocular clue of retinal disparity. The data suggest, moreover, that the contribution of the uniocular cues is significantly greater for some subjects than for others.

The findings of Holway's study may explain in part the lack of agreement in scores on different tests of binocular depth perception. In the Howard-Dolman test the uniocular depth clues based on vergence of the light rays and on subtense are in accord with the binocular disparity clue. In stereoscopic tests, on the other hand, there is no difference in vergence associated with the depth difference simulated by binocular disparity. If the test targets are of the same size, there is likewise no difference in visual angle associated with the difference in depth. In the Verhoeff Stereopter a conflict between the clues from visual angle and the clues from retinal disparity is deliberately introduced by making the more distant targets of greater width than the nearer ones.

The experimental findings of the present study support the view that uniocular clues may play a significant role in tests of binocular depth perception. Some subjects, for example, had significantly higher thresholds on the standard Stereopter than on a modified test in which there were no misleading uniocular size clues, and some with good scores on the Howard-Dolman test made poor scores on a stereoscopic test in which size and disparity clues were not in accord.

The tests investigated in this study agreed in from 79 to 92% of the cases in their classification of subjects as having either good or poor depth perception. Factors responsible for the discrepant findings and their relative frequency were as follows:

(*a*) Underestimation of ability to perceive depth. A false finding of poor depth perception was given frequently by the Vision Tester, and occasionally by the standard Stereopter, presumably because of a conflict between size and disparity clues. On the Howard-Dolman test, lack of skill or effort in making the necessary motor adjustments resulted in one instance in a false classification of poor depth perception.

(*b*) Overestimation of ability to perceive depth. Because of the short testing distance, both the stereopter tests gave false indications of good depth perception in the case of one subject with uncorrected myopia. In one case, poor depth perception caused by intermittent loss of binocular vision was not detected by the Howard-Dolman test.

The factors responsible for consistently poor depth perception on all tests were low visual acuity, suppression, tropia, and possibly heterophoria.

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CORTISONE IN LENS DISCISSION AND EXTRACAPSULAR EXTRACTION

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THE INITIAL INSIGHT

THE INITIAL insight from which this study proceeds arises from the case of L. S., a 38-year-old man whose left eye was accidentally penetrated by a carpet tack, with subsequent formation of a traumatic cataract. His injured eye was treated from the day of injury with 2 drops of 2.5% cortisone every two hours, and cortisone ointment 1.5% at bedtime, along with the usual adjuncts: atropine drops 1% twice a day, phenylephrine (Neo-Synephrine) drops three times a day, and sodium sulfacetamide ointment 10% at bedtime. For the first six days he received, in addition, sodium sulfacetamide drops locally and 300,000 units of procaine penicillin G daily. During the first 25 days of conservative treatment the eye became quiet, in spite of the presence of a considerable number of particles of lens matter in the anterior chamber, and the tension of the eye remained within normal limits. However, on the 25th night the patient complained of pain in the affected eye, and on the following day the tension in his left eye was found to be elevated to approximately 70 mm. of mercury. An emergency cataract extraction of the left eye was deemed advisable and was done on the same day, with success. Final corrected vision was 20/20.

The second patient, S. L. B., with a nuclear cataract complicated by posterior synechia due to an old iritis, had a cataract extraction. A moderate amount of cortex was left in the anterior chamber. A 0.5% cortisone solution was used topically every two to three hours, as well as scopolamine and sodium sulfacetamide drops. After two months there was complete absorption of the cortex and the posterior capsule was transparent, with 20/20 corrected vision resulting.

The third patient, M. L., had an extracapsular cataract extraction and was treated with 0.5% cortisone, starting on the fifth postoperative day. Subsequently, the cortical material left in the anterior chamber was completely absorbed, with 20/15 partial corrected vision resulting. The patient was seen again 10 months later, with iridocyclitis secondary probably to an infected tooth; this condition partially cleared after extraction of the tooth and treatment with 2.5% cortisone suspension. However, a secondary membrane formed after this inflammation.

This study was made possible by a grant from the Yale Medical Fluid Research Fund.
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These cases suggested the following problems for solution: What is the effect of cortisone on the reaction of the eye and on the absorption of lens material after discission or extracapsular extraction?

GENERAL BACKGROUND

In patients below the age of 35 years, the lens matter, including the nucleus, will be absorbed by the action of aqueous humor once a gap is made in the anterior lens capsule. Therapeutic use of this fact is made in congenital cataract, in which a discission is employed.

If an adjunctive agent, such as cortisone, were found to hasten absorption of remaining lens material and to subdue phacoanaphylactic irritation of the uveal tract, the extracapsular form of extraction would be at an optimum. The physiological mechanisms of cortisone in quieting inflammatory processes may be briefly considered. It is felt that the permeability of capillaries to proteins and cells in areas of inflammation is reduced. In allergy, cortisone acts not by blocking histamine at the receptor site but, rather, by the physiological compensation of reduced capillary permeability, with resultant inhibition of the symptoms and effects of allergy. The absorption of lens cortex does not depend directly on capillary permeability, but is the result of lysis of the cortex, in part by autolysis and in part by invasion of wandering cells. Cortisone greatly diminishes macrophage activity, and this factor may result in diminished absorption.

REVIEW OF THE LITERATURE

A survey of secondary works lying close to the field of this problem reveals the following points: Scheie and associates [1] reported two cases of persistent iridocyclitis due to retained lens material after attempted intracapsular cataract extraction. One patient presented large numbers of keratic precipitates. Both eyes were treated with cortisone applied topically, and both became white and quiet within four to seven days. Thorpe [2] reported the management of two cases of traumatic cataract with complicating phacoanaphylactic endophthalmitis. One patient, a man aged 40, had many keratic precipitates and considerable pericorneal injection, with lens matter in the anterior chamber. Ocular inflammation subsided considerably after 24 hours of parenteral corticotropin therapy. The other patient, a girl aged 16, had a moderate number of keratic precipitates and moderate pericorneal injection, with lens matter in the anterior chamber. Redness subsided in four days with topical use of cortisone drops, 0.5%, every hour while she was awake, and linear extraction was performed on the seventh day, with uneventful recovery. Similarly, Purnell and Leopold [3] reported that in three out of four cases of phacoanaphylactic uveitis the eye responded to local use of cortisone. Duke-Elder [4] added his observations on 34 cases of postoperative and post-traumatic uveitis treated locally with cortisone and cited an additional 37 cases in the literature, along with 22 cases available in the literature treated systemically. He summarized these cases:

> On the whole, the results, although variable, are good in this type of case. About 25 per cent of cases have shown little or no response, but most demonstrate an initial improvement. This applies equally when the inflammation is a simple post-traumatic reaction and when it appears to be due to the presence of lens substance in the eye after an extracapsular extraction of cataract or to a phako-anaphylactic reaction.

McLean and Gordon [5] treated immature senile cataracts in one woman for 11 days with a total of 1,250 mg. of corticotropin. There was no detectable change in the eyes. In addition, they observed no change in the various cataracts of 51 patients being treated with corticotropin or cortisone systemically for other conditions.

There appear to be three local complications in the use of cortisone in cataract surgery: (1) precipitation of glaucoma, (2) delay in wound healing, and (3) delay in absorption of postoperative hyphema.

McLean and Gordon [5] reported:

> Secondary glaucoma was precipitated in 4 out of 20 cases of uveitis and in 3 out of 13 cases of iridocyclitis while under systemic treatment. Five of these cases were treated with ACTH, 2 with cortisone.

Ashton and Cook [6] studied the effect of subconjunctival administration of cortisone upon the healing of through-and-through corneal wounds in rabbits: "Cortisone was found to inhibit the formation of the fibrinous coagulum, cellular infiltration, fibroblastic repair, and endothelial regeneration."

Benedict and Hollenhorst [7] reported an experimental procedure whereby eight rabbits received an injection of 0.2 cc. of their own blood into their respective right anterior chambers. Four of the rabbits were given 6 mg. of cortisone per day subconjunctivally. The other four were left as controls. In each case it became evident that "the rate of absorption of blood in the cortisone-treated animals was delayed as compared to the rate of absorption in the untreated animals."

OUTLINE OF EXPERIMENT

Thirty-one white rabbits were divided into four groups.

Group I (8 rabbits) were treated with cortisone by parenteral injection—20 mg. a day beginning 5 days after uniocular lens discission and continuing 14 subsequent days.

Group II (5 rabbits) were left untreated as controls following lens discission.

Group III (8 rabbits) were treated with cortisone by parenteral injection—20 mg. a day beginning within an hour after extracapsular lens extraction and continuing until the natural death of the animals.

Group IV (10 rabbits) were left untreated as controls following extracapsular lens extraction.

All rabbits were treated concurrently with atropine ointment 1% and sulfacetamide ointment 10% once a day as topical adjuncts.

The eyes were examined clinically every day postoperatively, and serial records were made at approximately one-week intervals. Readings of ocular reaction and degree of lens absorption were recorded on a 0 to 3+ numerical scale. The degree of ectasia in the eyes of the rabbits with extracapsular extractions was recorded on a 0 to 4+ numerical scale. (The term ectasia as used in this experiment denotes bulging of the cornea and/or bleb formation between sutures.)

Operative Technique.—Atropine drops 2% were used preoperatively for mydriasis. On 13 rabbits (Groups I and II) uniocular lens discissions were done in conventional manner, the lens substance being well broken up before withdrawing the needle. In each case, the anterior chamber retained its depth after the needle had been removed.

On 18 rabbits (Groups III and IV) uniocular extracapsular lens extractions were done. The posterior lens capsule and part of the anterior capsule remained, along with a slight amount of soft lens cortex. In four animals (two controls and two treated) only one-quarter of the lens matter was removed. This procedure was decided upon in order to produce a minor series of animals with a large amount of lens matter remaining after operation. In all cases iridectomy was performed and corneal-corneal sutures were used in closing the wound.

Diet.—The rabbits were fed Purina rabbit chow, a commercial preparation in the form of dehydrated compressed pellets. Fresh water was supplied daily. Added potassium was not supplied, and no attempt at salt restriction was made.

RESULTS

Groups I and II (Lens Discissions).—Sixty per cent of the control eyes showed marked lens absorption by the 19th postoperative day. None of the treated eyes showed pronounced absorption in the same period, although 25% showed moderate absorption. There was no significant difference in the inflammatory reaction between the two groups, since most of the eyes were quiet by the fifth postoperative day and remained so throughout the experiment.

Groups III and IV (Extracapsular Extractions).—A. There was heavy mortality in the rabbits of Group III after the 16th day of systemic cortisone treatment. The animals gradually lost their muscle mass; their fur became dull and thin, and they developed profound muscle weakness. The lower extremities, especially, seemed to be paralyzed toward the end of the period. Autopsy of two animals revealed no further gross pathology; this finding suggested that the cause of death was a metabolic derangement. The median value for survival time was 22 days. The mean survival time was 24 days, with a standard deviation of 7 days. The dose of cortisone used far exceeded the usual therapeutic level, but this high dosage was felt proper for the experiment.

B. The cortisone-treated animals showed slightly less reaction initially, but by the 14th day the two groups were similar. A secondary bacterial panophthalmitis developed in one cortisone-treated animal. The maximum reactions otherwise developed in those four eyes with only one-quarter of the lens matter removed. The eyes in which most of the lens matter had been taken out were relatively quiet in both treated and control groups.

C. In 75% of the cortisone-treated animals a significant degree of postoperative ectasia developed. Some of these had haziness of the cornea, separation of the wound edge, and bleb formation between sutures. None of the control animals had a significant amount of postoperative ectasia.

D. There was no significant difference between treated and control groups in autolysis of remaining lens material after extracapsular extraction under conditions of this experiment with the number of animals used. An incidental finding was that two of the cortisone-treated animals had small postoperative hemorrhages into the anterior chamber of the eye which failed to resolve. None of the controls had noticeable hyphema.

SUMMARY AND CONCLUSIONS

Systemic cortisone therapy does not increase the rate of absorption of lens material after lens discission or extracapsular extraction in rabbit eyes. There is some indication that cortisone therapy tends to block absorption of lens material from the anterior chamber.

From these experiments it is felt that the time-honored principle in good cataract surgery of removing a maximum amount of lens material during operation is more important than the effect of cortisone in prevention of postoperative inflammatory reactions.

Ocular complications of the use of cortisone after lens discission and extracapsular extraction include precipitation of glaucoma, delay in wound healing, delay in absorption of hyphema, and a decreased resistance to secondary infections.

ADDENDUM

A further pilot experiment using hydrocortisone in a small number of white rabbits has yielded the following inferences:

1. Hydrocortisone acetate has no noticeable effect in hastening recovery from reactions of the eye pursuant to extracapsular lens extraction.

2. Retrobulbar injections of hydrocortisone are to be avoided because of possible hemorrhage.

Mr. Arman Negri gave assistance in our work.

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PERIMETER WITH CONTROLLED ILLUMINATION AND RECORDING MECHANISM

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A. GENERAL CONSIDERATIONS

TO CREATE a perimeter in which precise visual fields may be obtained, all extraneous apparatus should be excluded from the patient. Only the point of fixation and the isopter should be within the range of vision. These points of fixation should be easily checked by the examiner while taking the field of vision, without his disturbing the patient.

In order to detect the early pathological changes induced by glaucoma, retinal disease, and abnormal factors affecting the intracranial portion of the visual pathway, even lighting upon the test object or target is necessary. Illumination of the perimeter must be equal in all meridians and should be controlled by the examiner so that any desired volume, in foot-candles, can be attained. The moving of the test object or target should be silent and have no distracting mechanisms. The examiner should be able to change the meridional position of the various isopters quickly and accurately.

The perimeter should be of sturdy construction, with ease of maintenance. No high lights should exist to disturb the patient at any point of position on the field of vision.

B. DESCRIPTION OF THE PERIMETER

The construction of this automatic type of perimeter is designed to insure the accurate measurements of the visual field.

1. *Dome.*—(*a*) Exterior Design: The perimeter dome (*A*) is constructed of black plastic, the interior of which has a dull, nongloss finish. The inside radius is 50 cm. The two flanges (*B*) are made to keep the rollers (*C*) in their alignment. The superior roller (*C1*) has a spring type of detent arrestor (*D*), which stops rotation of the dome at 30-degree intervals, and these inserts are painted white, with small decals showing their position, in degrees, to correspond with those of the recording paper. The two lower rollers (*C*) are supports of the plastic dome. The lower right roller is rotated with a small wheel (*G*) by the examiner to vary the positions of the test object. The recording mechanism is covered by a housing (*E*),

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Part II of thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, toward the requirement for the degree of Doctor of Science (D. Sc. [Med.]) for graduate work in ophthalmology.

attached to the apex of the dome, which is described under "Recording Mechanism."

(*b*) Interior Design: The interior of the dome has a recording tape arm set in a track which can be moved 90 degrees from the periphery to the center fixation. Upon the tip, or end, of the metal tape is a magnet (*Q*) to hold the varied sizes and colors of the isopters desired by the examiner. The point of fixation is in the apex of the dome, and a small white ring surrounds the center opening (*M*) so as to

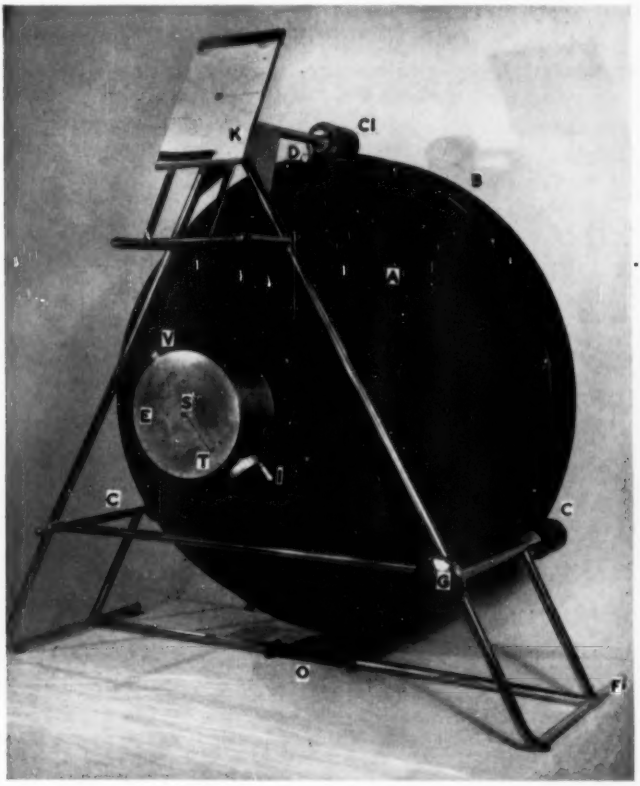


Fig. 1.—Raiford perimeter, back view. *A*, dome; *B*, flanges for rollers; *C1*, superior roller; *D*, detent arrestor; *E*, housing for recording mechanism; *G*, rotation wheel; *F*, tripod base; *O*, chin rest base; *T*, driving mechanism; *I*, hand crank; *V*, reel; *S*, marking indicator; *K*, platen for holding chart.

insure contrast for accurate patient fixation. The tube traversing the recording housing is to allow the examiner observation of the patient's eye position while taking the field of vision.

2. *Perimeter Base.*— The perimeter dome rests on a tripod, chrome-plated tube base (*F*). The rotation wheel (*G*) on the lower right (from the examiner's position) is turned in a clockwise movement, which eliminates any hysteresis of the dome movements. To the base portion there is attached the head rest (*H*), which

can be moved back and forth on a 70 mm. track to bring the right or left eye in alignment for the point of fixation (*M*). Elevation of the chin rest (*O*) can be adjusted to the facial variables of the patients to give the proper vertical point of center (*M*) at the dome.

3. *Illumination.*—The lighting source is from two small reflectors (*N*), each holding one 10-watt electric light. These two lamp reflectors are attached to the head rest (*O*). The light intensity on the test object is controlled by a rheostat (*P*), which ranges from 0.1 to 15 ft.-c. of illumination. This may be adjusted to

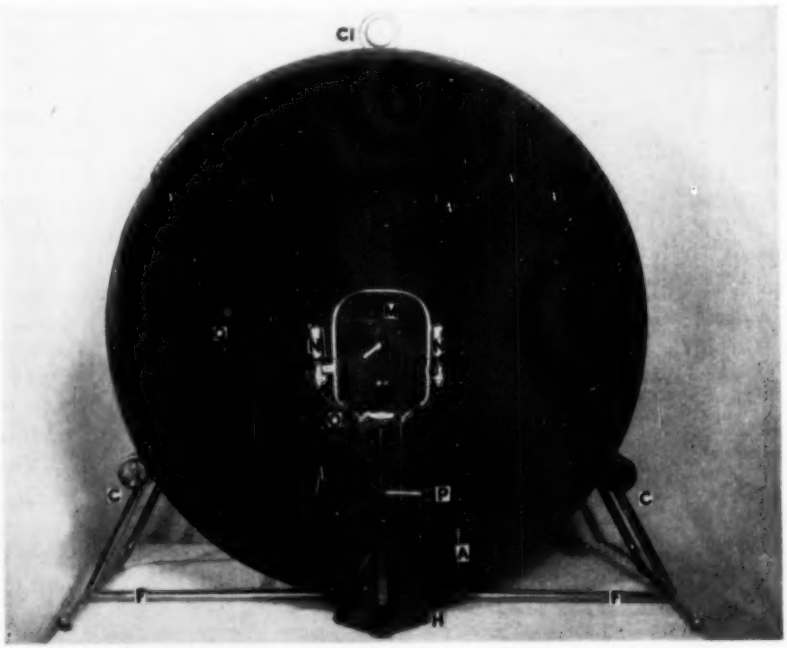


Fig. 2.—Raiford perimeter, front view. *M*, center fixation point; *Q*, magnet holding object; *N*, reflectors; *O*, chin rest; *P*, rheostat; *H*, head rest base; *F*, tripod base; *A*, dome.

an amount so desired by the examiner. The power for the light is through an extension cord to any 110-volt source.

4. *Recording Mechanism.*—(*a*) Housing: The housing (*E*) covers the gears of the recording mechanism. A hand crank (*I*) moves the target-gear-driving mechanism (*T*). This extends from a 20-tooth gear from the four-thread worm drive to the pinwheel opening on the perforated steel tape. The reel (*V*) takes up the tape, which has a small curve to eliminate any buckling. A magnet (*Q*) is attached to this recording tape on the interior of the plastic dome to hold the targets or test objects. The perforations of the tape not only connect the pinwheel but give it flexibility to travel smoothly within the internal housing track of the dome.

(*b*) Recording Device: From the hand crank (*I*) to the worm-gear drive (*T*) is connected the punch-point type of marking indicator. This moves in a 1:30 ratio through a slot, upon which is pressed the platen (*K*) holding the chart record for that field of vision.

(*c*) Chart-Holder Platen: The record chart is placed in the platen (*K*) in an inverted position and held in alignment by two clamps. When the patient views the test object, the platen is brought downward and a dot-like hole is made by pressure against the recording point (*S*). The center hole is placed over the fixation viewing tube.

(*d*) Electric Driving Mechanism: An electricity-driven motor in place of the hand crank (*I*) and dome rotator may be used with a reduction gear. Forward and reverse speeds, controlled by the examiner, are then used. One may be placed on the rotation wheel (*G*), which would give the perimeter full "push button" control.

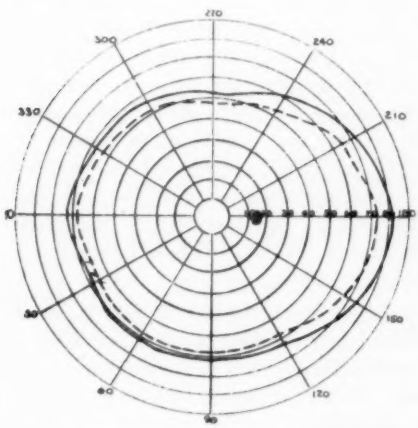


Chart 1.—Solid line indicates a normal visual field taken with the Raiford perimeter; the dotted line, the same visual field taken with perimeter B.

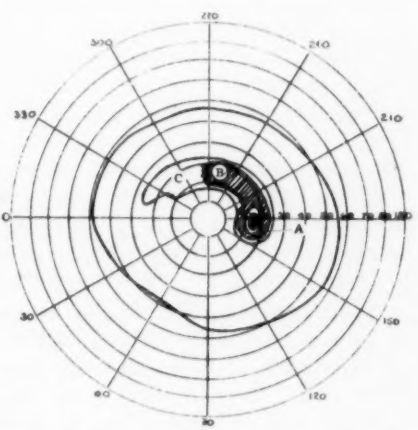


Chart 2.—*A* shows the right visual field without illumination control (with perimeter B); *B*, an increase of the arcuate scotoma revealed with a 5 f-c. illumination; *C*, field with illumination with the new type perimeter reduced to 2 f.-c.

SUMMARY

A. Clinical Evaluation of the Perimeter.—The visual fields in the normal and in several disease conditions were taken with the perimeter.

1. Normal: In this series, 22 visual fields were taken from 11 patients. The illumination was set at 5 f.-c. on the perimeter. A 2 mm. white test object was used on both the perimeters. The visual fields were first taken on the Raiford perimeter, and, after one hour's interval, on a regular perimeter (Perimeter B), utilizing the same technique in obtaining the peripheral fields. In comparing the two fields taken, the new perimeter gave its greatest value in the superior and inferior temporal quadrants. Perimeter B showed the least field change at the nasal borders in the area 30 degrees above and below the horizontal meridian.

Comparison of the two visual fields (Chart 1) showed that the new perimeter had an over-all enlargement. In the cases tested for comparison, the following value averages were obtained:

Meridian Positions, Degrees	New Perimeter, Degrees	Perimeter B, Degrees
0	62.5	58.7
30	57.2	55.6
60	60.4	56.7
90	61.2	58.2
120	62.4	59.8
150	72.0	68.5
180	81.1	74.0
210	74.2	65.2
240	60.3	53.4
270	52.5	48.3
300	55.0	52.8
330	57.6	55.5

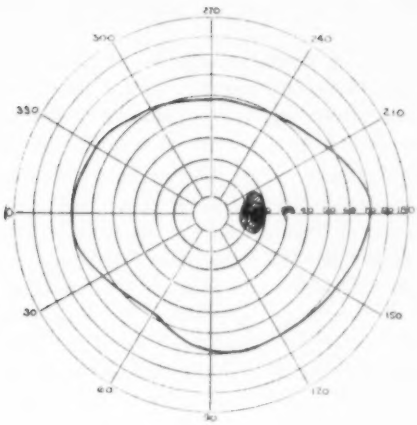
2. Glaucoma: The value and flexibility of this perimeter are manifested in the measurement of the fields of vision in cases of glaucoma. The opportunity to study the patient's clinical progress is invaluable when controls of technique and illumination can be maintained. Early cases, otherwise not detected, can be readily brought to their true value by reducing the illumination. The intensity and regularity of the enlarged blind spot (scotoma) may be accurately measured. This factor allows the ophthalmologist to evaluate the therapeutic responses in any given case, and a more accurate control of the patient's course can be assured. In Chart 2, *A* the right visual field was taken with perimeter B, without any control of illumination. In *B* an illumination of 5 f.-c. was maintained, which showed an increase in the arcuate scotoma. When the illumination was reduced to 2 f.-c. (Chart 2, *C*), the scotoma was increased in size.

3. Optic Nerve Pathology: The advantage of the perimeter is the ability of the examiner to control lighting of the desired foot-candle illumination. This is particularly valuable where there has been marked impairment in the papillomacular bundle fibers. Here, charting of the intensity of the scotomata can be accurately evaluated. Central fixation can be better maintained by the patient. External or peripheral distractions are shut off by the perimeter, and this is most important in cases of reduced visual acuity. The patient's apprehension is eliminated, thus producing finer measurement of the entire field.

Chart 3 shows a case of optic neuritis in which the field changes were not obtainable on a regular perimeter, owing to extraneous illumination, which caused patient confusion. In Chart 3 (O.D.) the comparison of the field with the new perimeter and that with perimeter B shows that a better evaluation of the peripheral field and scotoma was obtained.

In a case of compression of the optic nerves from craniostenosis (Chart 4), the new perimeter gave a very accurate evaluation of the left and right visual fields because the illumination could be increased and controlled. The left field could not be measured with perimeter B.

4. Macular Pathology: Disorders of the macula reduce the ability for central fixation, which varies according to the intensity of the disease. The patient's central fixation can be maintained far more accurately by reducing every possible extraneous stimulus. With this perimeter all outside interferences are reduced to zero, and only the target and its invisible carrier move within the patient's field of vision.



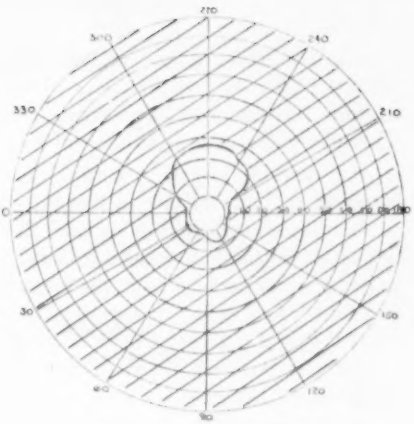
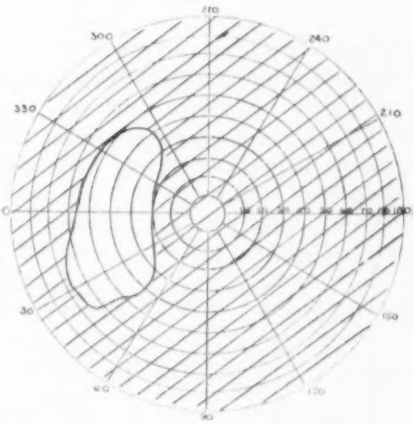


Chart 3 (Above, left).—Right visual field from a case of optic neuritis taken with the new type of perimeter.

Chart 4 (Above, right).—Compression of the left optic nerve from craniostenosis. The new type of perimeter gave a very accurate evaluation. Illumination could be increased and controlled. (Right) Visual field of the right eye.



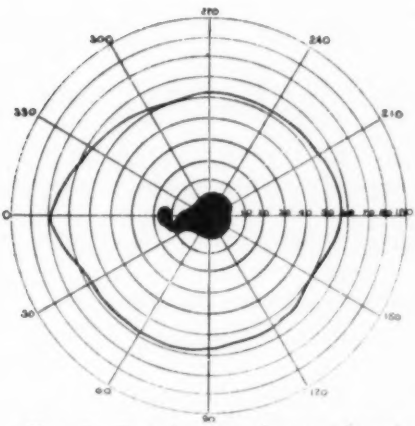


Chart 5.—Central scotoma in eccentric position from a case of Junius type of disciform macular degeneration in the left eye.

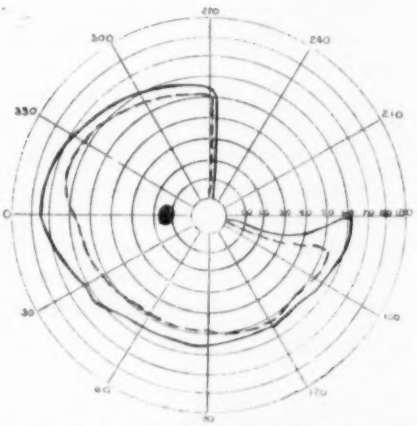


Chart 6.—Visual pathway pathology of vascular origin in the left eye. The smaller field (broken line) was taken with a regular perimeter; the larger (solid line) was taken with the new type of perimeter.

Chart 5 shows a case of the Junius type of disciform macular degeneration taken with the Raiford perimeter. The regular type of perimeter did not reveal the scotoma accurately in its eccentric position. Here, again, the patient's ability to concentrate upon a central point of fixation gave a truer picture of the visual field.

5. Visual Pathway Pathology: The full details of the field are more readily measured by reducing extraneous objects that enter the peripheral field. By having an unbroken nonreflecting surface, the areas of hemianopsia or quadrantanopsia can be more readily mapped out. The patient follows the target with greater ease and is not confused by any other movement. This is particularly important when the central fixation or papillomacular bundle fibers are involved in these lesions. Chart 6 is of a peripheral field, showing the use of the Raiford perimeter and that of perimeter B. Here, the visual field is better because of an unbroken nonreflecting background.

B. Mechanical Evaluation of the Raiford Perimeter.—1. The perimeter construction is of plastic, light-weight metal, and stainless steel. All moving parts are housed in a dust-proof cover. The dome may be constructed of spun aluminum instead of plastic, as in this model, thus eliminating the hysteresis sometimes experienced in molding plastic materials.

2. The use of a magnet to hold the test objects greatly simplifies the target carrier. This also facilitates the changing of the targets desired in any given examination.

3. The position of the two lights on the perimeter allows an even distribution of illumination.

4. By rheostat control the perimeter illumination ranges 1 to 15 f.-c. from the zero point.

5. The target and meridian positions can be fully controlled by electric motor operation. This gives the perimeter full "push button" operation by the examiner.

C. Advantage of Design.—The design of the perimeter offers the following advantages:

1. Controlled illumination, in tenths of foot-candles, allowing more accurate recording.

2. Standard control of isopter movement, enabling the examiner to present to the patient a steady, continuous, and accurate movement of the target.

3. More accurate isolation of the areas of scotomata, both relative and absolute.

4. More accurate recognition of early cases of conditions causing enlargement of the blind spot.

5. Elimination of extraneous distractions, allowing more accurate fields of vision and better patient cooperation.

6. Assurance of accurate records by use of the automatic charting device.

STREPTOKINASE-STREPTODORNASE (VARIDASE) IN TREATMENT OF CORNEAL ULCERS

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TILLETT [1] and his associates have demonstrated that a catalytic agent, streptokinase, and an enzyme, streptodornase * could be successfully employed as an adjunct in the treatment of certain conditions in which the accumulation of clotted blood and pus creates a barrier to therapeusis. These substances, which are elaborated by certain strains of beta hemolytic streptococci, offer a new physiologic approach to a difficult problem.

Christensen and MacLeod [2] feel that SK acts as a catalyst, causing the transformation of a zymogen of normal human blood, designated by them as plasminogen, into a proteolytic enzyme, plasmin. Plasmin is capable of digesting fibrinogen and lysing fibrin. There is some question, however, whether the activation of plasminogen by SK is one of catalysis. Ratnoff described this activation reaction as a stoichiometric one, complying with the law of mass reaction; i. e., plasmin activity is proportional to the product of the concentrations of both SK and plasminogen. This concept was recently confirmed by Wasserman.[3] SD is an enzyme which hydrolyzes deoxyribonucleic acid and deoxyribose nucleoprotein, which together constitute 30 to 70% of the sediment in thick, purulent exudates.[4] It is evident that the lysis of fibrin requires the presence of a serum factor (plasminogen). Magnesium (or manganese) must be available in order for the degradation of deoxyribonucleic acid to take place. Both these factors are usually present at the site in adequate amounts.

Since purulent exudates contain these two substrates, namely, fibrin and nucleoprotein, SK and SD would seem to be ideal agents to use in causing lysis and dissolution of this material. The protective covering of fibrin and pus can be removed from bacteria, so that they are exposed to the cellular defenses of the body. Contact between antibiotics and the invading organism is facilitated by the same process.[5] SK and SD have no effect on fibrous tissue and collagen. Normal living cells are not damaged by the enzymes. However, through local irritation to serous membranes, they cause an outpouring of both serum and cells.

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This work was originally submitted as a thesis to the faculty of the New York University Postgraduate School of Medicine in partial fulfilment of the requirements for the degree of Master of Science in Ophthalmology.

* In this paper, the symbols SK and SD are used for the terms streptokinase and streptodornase, respectively.

It has been shown by Johnson [6] that there is a decrease in the number of degenerated cellular forms following an injection of SK and SD into an inflammatory exudative area, whereas fresh viable cells are unaffected. There is also an increase in the number of active motile leucocytes. This cellular response contributes to the débridement by phagocytosis. Thus, these substances accomplish both enzymatic and phagocytic débridement.

SK and SD are foreign proteins and as such stimulate the formation of specific antibodies. These antienzymes can develop during an acute hemolytic Streptococcus infection or after repeated injections of these substances. Their inhibiting effect can be overcome by increasing the dosage of the enzymes. These agents can also produce systemic manifestations similar to foreign protein reactions. Elevation of temperature, headache, nausea, vomiting, malaise, and arthralgia have been noted. This reaction is evanescent, however, disappearing in 24 to 48 hours.[7]

Rapid fibrinolysis of fibrin coagulum of normal human blood is produced by SK. This is in contrast to its actions or delayed effect when tests are conducted using blood of other animal species.[7]

Many reports † have appeared in the literature which indicate that SK and SD have been used successfully in such conditions as decubitus ulcers, burns, wound infection, infected sinus tracts and fistulas, meningitis, osteomyelitis, hematomas, and chest conditions, e. g., hemothorax and empyema. Few reports have appeared in the ophthalmological literature.

Jukofsky [13] first reported the use of SK-SD in the treatment of hyphema and subconjunctival hemorrhage. He injected into the anterior chamber of rabbits various concentrations of SK and SD, together with approximately 0.4 cc. of the rabbit's own blood. He stated that concentrations of 50,000 units of SK had a favorable effect in lysing clotted blood in the anterior chamber of the rabbit's eyes. In concentrations higher than this, clouding, edema of the cornea, and iritis developed. A patient with traumatic hyphema and another with subconjunctival hemorrhage were then treated, with apparently good results. He also noted that topical application of 200,000 units of SK in the rabbit's eye caused no injurious effect but that a diffuse conjunctival injection ensued.

Friedman,[14] following the work of Jukofsky, treated three patients with hyphema by direct intraocular injection of SK-SD and two patients with subconjunctival hemorrhage with local injection of the drugs. In all five cases the results were disappointing. The reaction to the irritation of the SK was almost worse than the original condition. Severe endothelial damage, with subsequent corneal edema, cyclitis, secondary cyclitic membrane, and chronic inflammation, resulted in loss of useful vision, following intraocular injection. In one case enucleation was necessary because of secondary glaucoma and pain. The chemosis, lacrimation, photophobia, and pain which followed subconjunctival injection of SK-SD were far worse than the original subconjunctival hemorrhage. Cutting the dose in half, i. e., to 25,000 units, did not seem to remove the irritating qualities of the drug. We have found that concentrations as small as 5,000 units of SK, when injected into the anterior chamber of rabbits, produce a severe iridocyclitis and permanent damage to the cornea. It would appear, therefore, that SK and SD in the concentrations heretofore used are not safe drugs for intraocular use.

† References 8 to 12.

It seems that there is need for a physiologic débriding agent in the treatment of severe corneal ulcers in which a necrotic base and purulent exudate are present. With the foregoing facts in mind, the following experiment was undertaken, in which these agents were used as an adjunct in the treatment of corneal ulcers.

METHOD AND MATERIALS

Varidase ‡, the commercial name of a product containing SK and SD, comes in a white, sterile, powdered form and dissolves readily in water or saline. A buffer is included in each vial to maintain a pH of 7.5. The drug is relatively unstable when in solution and must be preserved at a temperature of +2 to +5 C. The Varidase used in this experiment contained either 200,000 units of SK and 50,000 units of SD or 100,000 units of SK and 25,000 units of SD.

Initially in the experiment, SK-SD was applied to the cornea by means of an eye bath, after the local instillation of 0.5% tetracaine (Pontocaine) hydrochloride. The concentrations of SK and SD used in the corneal bath experiment ranged from 8,000 and 2,000 units, respec-

Corneal Ulcers Treated with SK-SD (Varidase)

Case No.	Diagnosis	Culture	Method of Application	No. of Applications	Results
1	Hypopyon ulcer with descemetocele	Ps. aeruginosa	Corneal bath	10	Poor
2	Hypopyon ulcer perforated	M. lacunata	Subconjunctival injection	2	Poor
3	Hypopyon ulcer	None	Corneal bath	7	Poor
4	Hypopyon ulcer	M. lacunata	Corneal bath Drop instillation	3 11 days	Good
5	Hypopyon ulcer	M. lacunata	Corneal bath Drop instillation	2 1 day	Poor
6	Marginal ulcer	Negative	Drop instillation	4 days	Good
7	Recurrent central ulcer	Negative	Drop instillation	6 days	Good
8	Hypopyon ulcer with descemetocele	M. lacunata	Drop instillation	6 days	Poor
9	Hypopyon ulcer	D. pneumoniae	Drop instillation	7 days	Good
10	Marginal ulcer	Negative	Drop instillation	5 days	Fair
11	Recurrent central ulcer	M. lacunata	Drop instillation	6 days	Good
12	Hypopyon ulcer	M. lacunata Hemolytic Streptococcus	Drop instillation	6 days	Good
13	Hypopyon ulcer	M. lacunata Staph. aureus	Drop instillation	8 days	Fair
14	Hypopyon ulcer	M. lacunata	Drop instillation	7 days	Good

tively, to 100,000 and 25,000 units, respectively, per cubic centimeter of sterile water. The solution was held in contact with the ulcer for periods ranging from 5 to 20 minutes, administered once daily. It was prepared every day or every other day and stored at a temperature of from +2 to +5 C. Later the eye bath was discarded, and SK-SD (100,000 and 25,000 units respectively) was dissolved in 2 cc. of 1% methylcellulose, a fresh solution being prepared every other day. (The powder dissolves rapidly in methylcellulose.) This vehicle was selected because of its viscid nature, which allows more prolonged contact between the enzymes and the ulcer. Solutions of methylcellulose mix well with secretions, spread smoothly throughout the conjunctival sac, and remain longer in it than do aqueous solutions.[15] This solution was instilled into the patient's eye every one or two hours while awake.

One patient received subconjunctival injections of SK-SD dissolved in sterile water (5,000 and 1,250 units and 2,500 and 625 units, respectively) on two occasions.

The results of this experiment are summarized in the accompanying Table. The effect of SK-SD, as a débriding agent in corneal ulcers, was studied in 14 patients. Twelve of these patients had central ulcers, and 2 had severe ulcers of the marginal type. The causative organism was Moraxella lacunata (Morax-Axenfeld bacillus)

‡ Lederle Laboratories Division, American Cyanamid Company.

in six cases, Pseudomonas aeruginosa in one case, and Diplobacillus pneumoniae in another, and cultures were negative in three cases. In two cases mixed organisms were isolated—M. lacunata and Staphylococcus aureus in one and M. lacunata and a hemolytic Streptococcus in the other. One ulcer was not cultured. In addition to the enzymes, patients were given antibiotics topically, subconjunctivally, and systemically; cortisone, atropine, local heat application, and fever therapy were used as indicated. In several cases paracenteses were done when the intraocular tension was elevated.

The débriding action of these agents was determined by examining the patients daily with the biomicroscope. Every few days the corneas were stained with 1% fluorescein and studied to ascertain the amount of healing.

The results in seven cases were classified as good, in two as fair, and in five as poor.

The first patient treated with SK-SD had a hypopyon ulcer with descemetocele caused by Ps. aeruginosa. There was little, if any, clearing of the base of the ulcer with use of the corneal bath. The ulcer ruptured spontaneously, and the eye was enucleated five months later. In Case 2 SK-SD solution was injected subconjunctivally; the ulcer had spontaneously perforated before the injection. Since, in all probability, this eye was lost, a trial subconjunctival injection was justified. Two injections were given, without beneficial effect. This eye was enucleated four months later. Cases 3, 5, and 8 behaved in a similar manner; i. e., the base or margins of the ulcer did not clear and spontaneous perforation occurred.

The results in two cases were classified as fair. In one of these cases (Case 10), although the necrotic base of the ulcer cleared rapidly in three days, the ulcer ruptured spontaneously, and during the healing stage an adherent leucoma developed. In Case 13 a posterior abscess was present, and, although the ulcer cleared anteriorly, it did not heal until spontaneous perforation occurred and the abscess had drained. This perforation occurred in spite of repeated paracenteses.

In seven of the ulcers SK-SD seemed to have a definite beneficial, débriding effect. The effect was dramatic in Cases 7, 9, 11, and 14; the base of the ulcers cleared rapidly and the ulcers healed in a short time. In the other three cases (4, 6, and 12) the débriding action was somewhat less striking and the ulcers healed more slowly. Case 4 showed no improvement with the corneal bath. Treatment with SK-SD drops was then instituted and the bath discontinued; within five days the central portion of the ulcer had cleared. This ulcer, however, did not heal until five weeks later.

COMMENT

Admittedly, it is difficult to evaluate the results of this type of experiment, for several reasons. In the first place, several agents were employed at the same time, making it almost impossible to single out one agent as the effective one. Second, this evaluation is made more complex by lack of controls and/or corroborating animal work. Third, a small clinical experiment of this nature is not statistically significant.

It was considered unwise to assay a controlled clinical experiment because of the relative scarcity of this type of clinical material. Regarding animal work, the rabbit, which is the most logical laboratory animal to employ in such an experiment,

is low in the serum factor, plasminogen. Thus, SK would for all intents and purposes be ineffective and the potency of these substances considerably reduced.

No deleterious effects were noted when SK-SD was used topically. The corneal and conjunctival tissues tolerated high concentrations without obvious ill effect. When, however, it was injected subconjunctivally, even small doses proved highly irritating. Severe lid edema, chemosis, and marked pain developed about two to three hours after injection. Pain was never a complaint when SK-SD was used in drop form every one or two hours, nor was chemosis seen. Occasionally patients complained of slight pain after a corneal bath application. Some eyes were somewhat more congested while under SK-SD therapy. There was no accumulation of purulent exudate in the conjunctival sacs and along the lid margins while patients were treated with SK-SD, and in general the affected eye appeared "cleaner." In one patient, whose case report is not included here, subconjunctival injection produced marked systemic symptoms, consisting of nausea, vomiting, and a temperature of 104.2 F., all of which subsided within 36 hours.

The results with the corneal bath were disappointing, although more frequent daily application might have produced better results. Eareckson and associates [16] reported the effective débridement of a corneal ulcer with an SK-SD eye bath applied every four hours for three days. This method, nevertheless, is cumbersome at best and, if used at frequent intervals, is even dangerous in patients with descemetocele.

Drop instillation was found to be a satisfactory method of administration, although more prolonged contact between the ulcer and the enzymes could possibly be accomplished by using an ointment vehicle. The ointment, on the other hand, might act as a barrier to the antibiotics, which would limit its usefulness.

It can be noted from examination of the Table that 8 out of the 14 ulcers were caused by M. lacunata. This organism, as a cause of hypopyon ulcer, was recently elaborated on by Fedukowicz and Horwich.[17] This type of ulcer is particularly resistant to therapy.

SK-SD has been used in eye wards of our institution for two years in the treatment of corneal ulcers. It has not been used routinely in all types of ulcers but has been employed only in those in which the base contained much necrotic material and thick purulent exudate was present. Patients were kept on SK-SD as long as the ulcer continued to clear, or until it became obvious that this treatment was ineffective. In most cases this period was about six or seven days.

Cases were not graded according to visual results, since central ulcers usually heal with a dense scar and vision is ordinarily not equal to more than counting fingers. In spite of the expected poor visual result, it is important to preserve the integrity of the eye by (1) preventing perforation of the ulcer and subsequent development of adherent leucoma and (2) preventing posterior synechiae, so that a functioning pupil is maintained. Thus, the eye becomes a better surgical risk for keratoplasty if such a procedure becomes indicated at a later date.

While only one-half the cases (7 out of 14) showed good results, it should be mentioned that three of the ulcers classified in the poor category were far advanced before treatment was begun. Descemetocele was present in Cases 1 and 8, and in Case 2 the ulcer had previously perforated.

It is suggested that the following routine be established in the treatment of severe hypopyon ulcer:

1. Smear, scraping, culture, and sensitivity tests.

2. Dilatation of pupil with 2% atropine, 4% cocaine, and 10% phenylephrine (Neo-Synephrine) hydrochloride pledgets in both fornices. If use of the pledgets is unsuccessful, then a combination of drugs should be injected subconjunctivally. This is indeed important, because unless dilatation is attempted when the patient is first seen, it may later be unsuccessful. If the pupil does not dilate with this treatment, the synechia cannot be broken by medical means.

3. Instillation of SK-SD (Varidase) in 1% methylcellulose, one or two drops every one or two hours.

4. Systemic administration of chloramphenicol (Chloromycetin), sulfonamides, penicillin, or streptomycin, or combinations thereof, as indicated.

5. Subconjunctival injection of penicillin and streptomycin if necessary.

6. Topical administration of appropriate antibiotics.

7. Local application of heat three times a day.

8. Fever therapy.

CONCLUSIONS

No definite conclusions can be gathered from such a small clinical experiment, but certain impressions have been gained. In corneal ulcers, in which there is need for débridement, it is suggested that SK-SD (Streptokinase-Streptodornase; Varidase) be used as an adjunct to suitable antibiotic therapy. If the ulcers are severe, it is wise to treat the patient with the appropriate antibiotics systemically and subconjunctivally. The intraocular and subconjunctival injection of SK-SD is unsafe in the concentrations heretofore used.

SUMMARY

Fourteen patients with corneal ulcers were treated with SK-SD (Varidase) and antibiotics.

In seven cases the results were good; in two, fair, and in five, poor.

The use of SK-SD, as an adjunct to antibiotic therapy, is suggested in severe corneal ulcers.

The injection of SK-SD intraocularly or subconjunctivally is not advised.

A routine in the treatment of severe corneal ulcers is outlined.

Dr. A. Gerard DeVoe and Dr. William S. Tillett gave helpful suggestions during the course of this experiment.

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A NEW CAMERA FOR MEDICAL STEREOPHOTOGRAPHY WITH SPECIAL REFERENCE TO THE EYE

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DESPITE its obvious advantages, three-dimensional photography of the eye has been infrequently employed.* A special camera for this purpose was described by me several years ago.[6] Subsequent models utilizing the same basic principles have now been used in the Howe Laboratory of Ophthalmology for five years, but the modifications have been sufficiently extensive to warrant designating the present model as a new camera.

The advantages of the present camera, leading to simpler operation, are these: (1) a new device for more accurate focusing; (2) a single film holder; (3) a more compact construction; (4) a wider range of magnification with a single focal length lens, and (5) a reflex mirror system. It retains the advantages of parallax correction without distortion (by translation), variable interlens distance, and the use of electronic flash (Strobe light). Although this camera was primarily designed for use in photography of the anterior segment and lens of the eye, it has also been found useful in other medical and biological fields.

DESCRIPTION

The basic components of the camera are (1) the prism-lens assembly, (2) the reflex housing, (3) the film holder, (4) the electronic flash lamp for the source, (5) the base, and (6) the stand with rack and pinions. The prism-lens assembly (Fig. 1, *A*) is composed of two rhomboid prisms (Fig. 2, *E*), one mounted in front of each lens (Fig. 2, *D*). The rays entering the camera are first reflected through these rhomboid prisms, which are arranged on two right- and left-hand threaded screws. This arrangement makes it possible to move the upper two reflecting surfaces toward or away from each other without linear movement of the lower surfaces. In turn, the lower reflecting surfaces can be moved without movement of the upper surfaces. The separation of the upper two reflecting surfaces determines the effective interlens distance, and the separation of the lower surfaces determine the correction for parallax. The lower two surfaces of the rhomboid prisms face two matched photographic lenses (Fig. 2, *D*). These lenses are also connected with the prisms in such a way that movement of the lower surfaces produces a corresponding movement of the lenses. A pair of round bellows connects the lenses with the reflex housing. The reflex mirror, when down, is light-tight and thus also acts as a shutter (Fig. 2, *C*). Incorporated in the roof of the double reflex housing (Fig. 1, *F*) are six incandescent bulbs, which are used in focusing the camera. These consist of four small bulbs of the "point source" type (Fig. 2, *B*) and two larger bulbs having vertical filaments (Fig. 2, *A*). All the filaments are located so as to be effectively in the plane of the film, and thus their images are projected by the optical system of the camera onto the object being photographed (Fig. 2, inset). The larger bulbs are centrally located above each reflex mirror

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

* References 1 through 5.

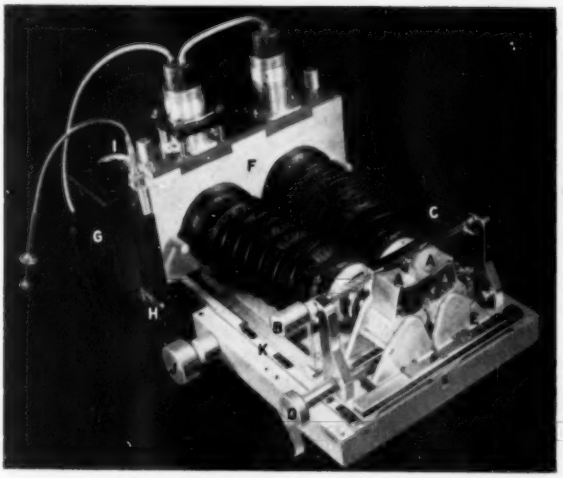

Fig. 1.—The stereoscopic camera with the electronic flash unit removed, demonstrating (*A*) prism-lens assemblies, (*B*) interlens adjustment knob, (*C*) interlens adjustment scale, (*D*) parallax adjustment knob, (*E*) parallax adjustment scale, (*F*) reflex housing, (*G*) spring mechanism housing, (*H*) lever arm, (*I*) film advancement knob on the film holder, (*J*) bellows extension knob, and (*K*) bellows extension scale.

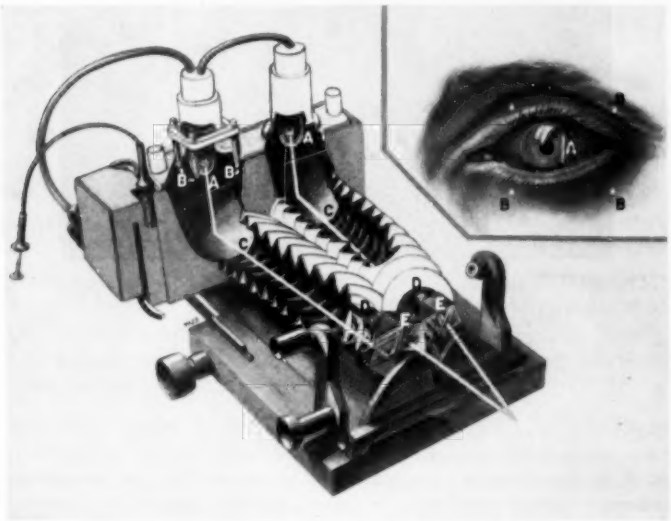

Fig. 2.—Semidiagrammatic drawing of the camera showing the optical system. Represented is the projection of the images of the focusing lights when the mirrors are in the downward position. The inset illustrates the relative positions of the "field" lights and the center focusing lights. The latter are in alignment on the iris. *A* indicates center focusing lights; *B*, corner "field" lights (paths of which have not been demonstrated), *C*, reflex mirrors, *D*, lenses and *E*, rhomboid prisms.

(Fig. 2, *C*). Their vertical filaments are placed in such a manner that one image is projected above that of the other. When these images are in alignment with each other on the object being photographed, the camera is in accurate focus (Fig. 2, inset). The smaller bulbs are located above only one reflex mirror, with one bulb in each corner of a rectangle equal to the size of the film. By means of these smaller bulbs the limits of the field of the picture are exactly defined on the object being photographed no matter what magnification or minification is used (Fig. 2, inset).

Mounted on one end of the reflex housing is the spring mechanism (Fig. 1, *G*), which is activated when the cable release is pressed. The reflex mirror is lifted to the horizontal position, and at this point a microswitch is activated, which, in turn, triggers the electronic flash. The mirror then immediately returns to its light-tight position. In addition, the mechanism automatically turns off the focusing lights when the cable release is first pressed. These lights remain off until the lever arm (Fig. 1, *H*) is returned to its downward position. After each exposure the lever arm is locked in the upward position and cannot be lowered until the film has been advanced. This avoids double exposure.

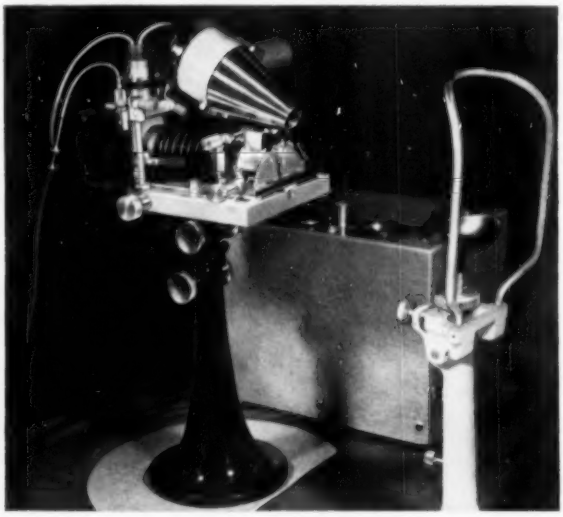

Fig. 3.—Complete camera ready for operation. Unit consists of camera, flash lamp with cone, power supply, and chin rest.

The film holder is attached to the reflex housing and carries the standard 35 mm. films. The resultant picture size is 24 by 30 mm. (approximately 1 by 1¼ in.) for each picture of the stereo pair.

The electronic flash unit consists of a flash lamp (General Electric FT218) mounted in front of a 2 in. (5 cm.) concave reflector (Fig. 3). A small polished metal cone is mounted on the front of the lamp housing. The smaller end of this cone is just above the two prisms. Because the lamp housing is mounted on the camera, the lamp remains in alignment regardless of camera movement.

The reflex housing, with the film holder, and the prism-lens assembly are mounted on a base. Bellows extension is accomplished by the forward and backward movement of the reflex housing by means of a rack and pinion. The base is mounted on a stand, allowing linear movement of the entire camera forward, backward, upward, and downward. It also allows rotation in both a horizontal and a vertical plane. When utilized for photographing the anterior segment or lens, the camera, with its stand, is placed on a small table, to which a chin rest is attached. The power supply is conveniently placed on a small shelf under this table.

The camera is calibrated by means of three scales that show, respectively, (1) the amount of bellows extension, which determines the magnification (Fig. 1, *K*); (2) the separation of the upper reflecting surfaces of the rhomboid prisms, which determines the effective interlens distance (Fig. 1, *C*), and (3) the separation of the lower reflecting surfaces, which determines the parallax adjustment (Fig. 1, *E*). Each scale has engraved on it numbers which represent the degree of magnification or minification.

The lens aperture remains set at *f*/18 at all times, and the light intensity is varied for the various magnifications. This light intensity is charged by means of a variable transformer and a voltmeter, which are built into the power supply. The meter is calibrated according to the degree of magnification and minification corresponding to the scales on the camera. This meter reading is adjusted by means of the variable transformer knob on the power supply.

OPERATION

Depending on the requirements of detail and area, an appropriate magnification or minification is selected. Adjustment for interlens distance, parallax correction, and bellows extension is accomplished by setting each of the three calibrated scales to the number representing the desired magnification. Adjustment for light intensity is determined by the meter reading on the power supply. Thus, if a magnification on the film of 1½× is required, each scale is adjusted to the number 1½. Next, the lever arm is moved to the down position, turning on the focus lights, which are projected onto the object being photographed. The entire camera is then moved toward or away from the object by means of the rack and pinion until the images of the vertical filaments are in alignment. By noting the positions of the images of the four small bulbs, one is able to determine the extent of the field, each light representing one corner of this field. At the moment the two images of the centrally located lamps are seen to be in alignment the cable release may be pressed. This will lift the mirror and trigger the electronic flash. To repeat the cycle, the lever arm must be returned to its downward position. This cannot be accomplished, however, until the film is wound to the next frame.

COMMENT

The difficulties encountered in close-up stereophotography are largely those of correcting the parallax and varying the interlens distance. It is essential that the area incorporated in each of the stereo pairs be closely approximated. This correction for the marked parallax produced by the closeness of the objects being photographed is accomplished, as already mentioned, by movement of the lower two reflecting surfaces of the rhomboid prisms toward or away from each other. Failure to correct for this would result in duplication of only a portion of the fields in each of the stereo pairs. As such, they would be unsuitable for stereoscopic viewing. Also, by keeping the plane of the film parallel with that of the object, as is the case with this camera, correction for parallax is accomplished by translation. This avoids the undesirable "keystoning," or wedge-shaped distortion, associated with correction for parallax by convergence.

It is a known fact that an interlens distance of less than the average interocular distance is required for stereophotography of close-up objects. Thus, in the equipment described, an effective interlens (actually interprismatic) distance of 18 mm. is used at a magnification of 2 × on the film (or 10 × in the viewer). It has been determined that this effective interlens distance at 2 × magnification is required to obtain a realistic stereoscopic effect of the human eye. Greater or smaller lens separations may be required, depending on a number of factors. Some of these factors are the distance of the camera from the object being photographed, the depth within this object, the focal length of the camera lens, and the method of viewing the stereoscopic photograph (viewer or stereoprojector). At the higher magnifications the

interlens distance should be less than that possible by placing most photographic lenses side by side, because of the increased diameter due to the barrel in which the lens is mounted. Thus, the arrangement using rhomboid prisms not only enables one to adjust for parallax but also makes possible an effective interlens distance considerably less than the diameter of the mounted lens. Under these conditions, the faces of the prisms need be only large enough to cover the area of the actual lens itself, which is generally about one-half the diameter of the complete lens with its mount. Therefore, with the considerably decreased effective interlens distance, the camera has a continuous range of focusing from a magnification of 2½ × on the film (13 × viewer magnification) to a minification which will include, for example, the full length of a patient.

One of the more important aspects of medical or biological photography is an accurate method of focusing. It is preferable, and sometimes essential, to avoid the use of bright lights in focusing and to avoid having to close the apertures after focusing. Owing to the sensitivity of the eye to light, especially in the diseased state, frequently only a minimum of light is tolerated. Moreover, because of the difficulty of immobilizing many living objects, it is important to be able to take the photograph immediately at the completion of focusing. The described method of focusing fulfills both these requirements. The focusing lights place a very small total amount of light in the eye, although the images of the aligned filaments are very bright. Moreover, focusing by means of alignment of the filament images is actually more accurate when the lens apertures are small (*f*/18 being used). In addition, the reflex mirror system provides for practically zero delay between the focusing and the taking of the picture.

Another advantage of this method of focusing is that the images of the filaments are seen in the media of the eye in the same manner as the slit-lamp beam is seen. These images can, for example, be aligned in any portion of the crystalline lens, even though the lens has no visible opacities. Also, in focusing, it is generally much easier to determine the correct angle of view when looking directly at the object being focused upon than through some type of viewer.

An alternative method of focusing is made possible by the double-reflex mirror system. The focusing lights are removed and the two images viewed stereoscopically on a ground glass by means of a pair of lenses identical with those used in the stereoscopic viewer. A pair of roof prisms are used in this viewer to correct for reverse stereopsis. By means of this arrangement a stereoscopic effect is produced which is very similar to that which will result in the final picture. In this way various combinations of effective interlens separation and parallax adjustment can be tried until the desired effect is obtained. This is especially advantageous when objects are being photographed which have an unusual degree of depth. Correction can be made for objects which are unusually shallow and require an increased interlens separation or are unusually deep and thus require a decreased interlens separation. In addition, it is not necessary to guess the proper settings in photographing objects with which one has not already had experience. If considered desirable, the depth can be exaggerated, thus producing a hyperstereoscopic effect. This method can be utilized to bring out important depth relationships, such as the difference in depth of various opacities within the cornea. To produce this effect, an increased effective interlens separation must be used. This ground glass method of focusing just described, how-

ever, necessitates having the apertures open, as well as a fairly bright illumination of the object being photographed.

Regarding lenses, it has been found that for maximum definition a symmetrical type of lens designed for focusing at close range is the most desirable. Of this type, the 80 mm. Microsummar f/4.5 (E. Leitz, Wetzler) is particularly suited because of its small amount and its longer focal length. This lens allows an easier working distance between the camera and the patient when the higher magnifications are used. The 3½ in. Goerz Dagor f/6.8 (Goerz American Optical Co.) is another symmetrical lens, with the additional advantage of a removable element which increases the focal length. This makes possible the taking of photographs at a 1:1 magnification with more than 1 ft. (30 cm.) distance between the patient and the camera, a feature particularly valuable in photographing eye operations. Because a considerable portion of the stereoscopic photograph must be in focus to achieve a desirably realistic effect and to avoid discomfort in viewing, a small aperture is absolutely essential. However, it is important to have a lens of moderate speed in order that the original calibration can be accurately accomplished or that the ground glass method of focusing can be utilized. Thus, with a lens of moderate speed, the calibration of the higher magnifications can consistently be made accurate within 0.2 mm. of the point of the actual focus. Focusing by means of the alignment of the filaments is also repeatable within 0.2 mm. with the apertures closed down. Thus, the maximum error in focusing is somewhat less than 0.4 mm., and the depth of the field is approximately 3 mm. at 2 × magnification (on the film) with an aperture setting of f/18. Because the critical aperture is considerably exceeded if the lens is stopped down much more than f/18, it appears that this aperture setting is about optimum.

The electronic flash lamp (Strobe light), now commonly used in medical photography, is particularly well suited to the eye because of its short duration (approximately 1/5000 second), ease of use, and safety. In anterior segment photography a large corneal reflex often obscures important details and is also disturbing to the person viewing the photograph. Therefore, it is important to take measures to reduce to a minimum the size of the reflex. This must be done without sacrificing too much light in order that a small aperture can be utilized. Both by mounting the flash lamp in front of a small reflector and by keeping the light source well away from the eye, this reflex can be kept small. Both the General Electric FT210 (with the envelope removed) and the General Electric FT218 appear to be the most satisfactory for this purpose. It has been found that anything less than a 200 watt-second power supply produces an inadequate amount of illumination for color film.

The stereoscopic photographs taken with this camera may be viewed or projected with an ordinary stereoscopic viewer or projector. A special viewer utilizing a 4-watt fluorescent lamp and fixed focus system has been found to have definite advantages over those commercially available.

SUMMARY

It is generally agreed that there are features in medical photography, especially in eye photography, which cannot be adequately shown without the stereoscopic photograph. The present camera takes stereoscopic photographs of close-up objects and utilizes independent variable interlens separation and parallax adjustment. This important feature eliminates the common distortions inherent in other cameras. It

has a range of focusing which will include an area slightly less than the cornea (2½ × magnification on the film) to an area which would take in the full length of a patient. The camera utilizes a single film holder in combination with a double reflex housing and an electronic flash lamp (Strobe light). The images of six small lights are projected onto the object being photographed by means of the optical system of the camera. Four of the lights are of small "point source" type and are projected to each corner of the field and delineate its extent. The other lights are centrally located and have vertical filaments. When the images of these vertical filaments are in alignment on the object being photographed, the camera is accurately focused. This procedure is performed with apertures stopped down, and the picture can be taken immediately at the completion of focusing. The operation of the camera is simplified so as to make possible the setting of the camera for the desired magnification and the taking of the picture within a minute's time.

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EFFECT OF CHANGES IN OSMOTIC PRESSURE OF BLOOD ON AQUEOUS HUMOR DYNAMICS

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THE OSMOTIC relation between blood and aqueous humor is a factor which plays an important and well-recognized part in governing the intraocular pressure.[1] Duke-Elder [2] and associates showed in 1938 that the aqueous is slightly hypertonic to blood; this observation was further elaborated by Duke-Elder [3] and Davson [4] and substantiated by Kinsey.[5] In 1948 Duke-Elder and Davson [3] wrote: "It may be that the maintenance of this osmotic gradient is of considerable importance in the mechanism of the intraocular pressure. This factor has not been fully explored." A unified concept for the maintenance of the intraocular pressure was proposed by Kinsey [6] in 1950; here, again, emphasis was on the osmotic interrelationship of blood and aqueous humor. The attention of the above-mentioned investigators was focused mainly on the intraocular pressure, while other aspects of aqueous humor dynamics were not explored. The introduction of Grant's * aqueous outflow test gave a new impetus to glaucoma research, because it furnished us with more information concerning the pressure regulation mechanism of the eye; i.e., in addition to the intraocular pressure, we can now measure the resistance to the outflow of the aqueous and also calculate the total rate of aqueous outflow. Because of the apparent importance of the osmotic gradient existing between the intraocular fluid and the blood, it was thought that by employing Grant's tonographic method and artificially changing the osmotic pressure of the blood, further information might be obtained concerning the aqueous humor dynamics of both normal and glaucomatous eyes. With this idea in mind, the following study was undertaken.

MATERIAL AND METHODS

The majority of the patients for this study were taken from the Glaucoma Department of the Institute of Ophthalmology of the Presbyterian Hospital in New York; the rest of the patients were obtained from the Glaucoma Clinic of the Institute of Ophthalmology in London. All patients had well-documented histories of glaucoma dating back anywhere from several months to several years. For the purposes of the present discussion, chronic simple, or open-angle, glaucoma will be defined as a disease characterized by increased intraocular pressure, glaucomatous field changes, and cupping of the optic nerve head, the anterior chamber angle being open at all times. The glaucomatous eyes had not been operated on and were without miotic

This study was supported by the Alfred P. Sloan Foundation, Inc., and by the Whitehall Foundation, Inc.

From the Institute of Ophthalmology, Presbyterian Hospital, and from the Glaucoma Clinic, Institute of Ophthalmology, London; Director of Research, Sir Stewart Duke-Elder.

* References 7 and 8.

medication for at least 36 hours prior to the experiment. Tensions were taken by the electronic tonometer, and the aqueous outflow test was carried out according to Grant's [9] four-minute test, all measurements being performed by the same observer. The facility of aqueous outflow, which is a measure of the resistance to the outflow, is expressed as a coefficient, *C*, or cubic millimeters per minute per millimeter mercury pressure, and the total rate of flow, as *K*, or cubic millimeters per minute. A series of normal eyes were also studied; the normal subjects were in approximately the same age group as the glaucomatous patients.

Eyes with congestive, narrow-angle glaucoma were not included in this study because it is known that the size of the pupil and the appearance of the anterior chamber angle influence the intraocular pressure in this type of glaucoma. Consequently, any effect produced by varying the osmotic pressure of blood may be overshadowed by the momentary state of the anterior chamber angle in these eyes. In chronic simple, open-angle glaucoma, on the other hand, the size of the pupil and the state of the angle probably have only a minimal effect on the pressure regulation mechanism of the eye.

The use of tonography on human eyes introduces certain sources of error. This problem was extensively discussed by Becker and Friedenwald [10] in a recent paper. The limitations of the method are particularly noticeable when absolute values are considered, i. e., when the results of tonography for one patient are contrasted with those for another. However, the results become considerably more significant when this test is performed by the same observer, using the same electronic tonometer on the same eye. It is to be expected that the error that occurs in tonography probably will be constant in a given eye within a limited period of time, and therefore the relative changes that take place become of importance. In this investigation, these relative changes in the tonographic measurements were primarily considered. Furthermore, it should be mentioned that Grant † first described the aqueous outflow test not as a diagnostic procedure, but mainly as a clinical method to study the mechanism of glaucoma. Since that time, however, the aqueous outflow test has been used primarily as a diagnostic ‡ and prognostic procedure in glaucoma. In the present investigation, on the other hand, tonography was employed for its original purpose, namely, to study the mechanism of primary glaucoma.

Sorbitol § was chosen as the hypertonic agent to be injected intravenously. Bellows and associates ‖ did extensive studies on the effect of various hypertonic solutions, particularly sorbitol, on the intraocular pressure of glaucomatous eyes. Sorbitol appears to be relatively nontoxic and only partially metabolized, as most of it is excreted unchanged from the body; it can be used with impunity even in moderately diabetic patients. For the purpose of the present work, 100 cc. of 50% sorbitol was injected intravenously within five minutes; the intraocular pressure and tonographic measurements were carried out at various intervals before and after injection.

In order to study the effect of hypotonic agents on aqueous humor dynamics, the water-drinking test was performed on a group of normal eyes. It is known that water will cause hemodilution and thereby reduce the osmotic pressure of blood. This test was carried out on an empty stomach, tonographic measurements being done both before and approximately half an hour after the ingestion of 1,000 cc. of water.

In a previous communication [18] the spontaneous diurnal variations in intraocular pressure were studied with the aqueous outflow test in a group of glaucomatous eyes. At that time only the facility of aqueous outflow was reported; however, in the light of knowledge gained from the present study, it became of interest to examine the effect of spontaneous diurnal changes on the total rate of aqueous outflow as well. Therefore, the results of the previous study were reevaluated, and it was found that of the 40 eyes with chronic simple glaucoma studied with tonography, 22 showed considerable changes in the intraocular pressure and also in the total rate of aqueous outflow. For this reason, the spontaneous diurnal changes in the total rate of flow of aqueous in these glaucomatous eyes will be given in the present report.

† References 7 and 8.

‡ References 11 through 15.

§ Sorbitol was supplied by Abbott Laboratories, North Chicago, Ill., through the courtesy of Dr. Arnold E. Osterberg.

‖ References 16 and 17.

RESULTS

Figure 1 shows the effect of intravenous injection of sorbitol on the aqueous humor dynamics of eyes with chronic simple glaucoma without medical or surgical treatment. It is evident that in most of these eyes there was considerable drop in the intraocular pressure within half an hour. Preliminary experiments showed that the greatest fall in the tension of these eyes occurred approximately half an hour after injection; the tension then slowly began to rise and in most instances attained the original level within two hours. At the same time, however, the facility of aqueous outflow remained approximately the same, the minimal changes noted being within

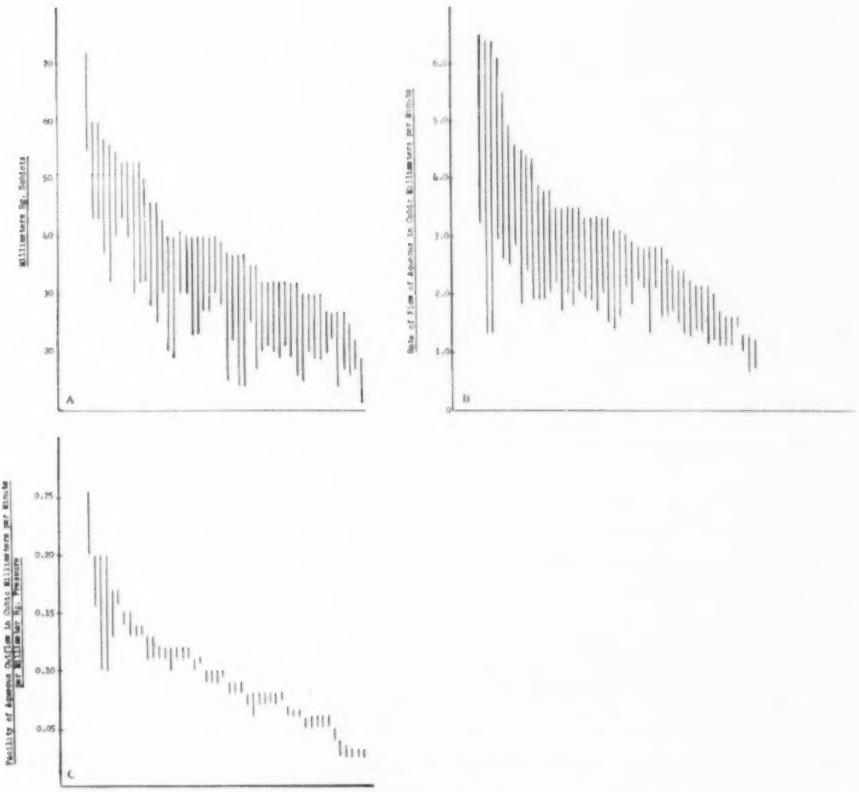

Fig. 1.—*A*, effect of intravenous injection of 100 cc. of 50% sorbitol on the intraocular pressure in 48 eyes with chronic simple, open-angle glaucoma not treated or operated on. Each vertical line represents the change in intraocular pressure from just before to 30 minutes after the test in an individual eye.

B, effect of intravenous injection of 100 cc. of 50% sorbitol on the rate of flow of aqueous in 48 eyes with chronic simple, open-angle glaucoma not treated or operated on. Each vertical line represents the change in the rate of flow of aqueous from just before to 30 minutes after the test in an individual eye.

C, effect of intravenous injection of 100 cc. of 50% sorbitol on the facility of aqueous outflow in 48 eyes with chronic simple, open-angle glaucoma not treated or operated on. Each vertical line represents the change in the facility of aqueous outflow from just before to 30 minutes after the test in an individual eye.

TABLE 1.—*Effect of Intravenous Injection of 100 Cc. of 50% Sorbitol on Facility of Aqueous Outflow, Total Rate of Flow, and Intraocular Pressure in a Patient* with Established Bilateral Chronic Simple, Open-Angle Glaucoma That Had Not Been Operated On and Had Had No Miotic Medication for Forty-Eight Hours Prior to Test*

	O.D.†			O.S.†		
Time	C	K	I.O.P.	C	K	I.O.P.
8:15 a. m.	0.13	4.2	37	0.15	3.8	30
8:30 a. m.	100 cc. of 50% sorbitol injected intravenously					
9:00 a. m.	0.14	1.9	15	0.14	1.9	15
9:50 a. m.	....	...	23	....	...	23
10:10 a. m.	....	...	32	....	...	27
10:30 a. m.	....	...	33	....	...	29
11:00 a. m.	0.13	3.6	32	0.15	3.5	27

* Mrs. A. W.

† C indicates cubic millimeters per minute per millimeter Hg pressure; K, cubic millimeters per minute, and I.O.P., millimeters Hg intraocular pressure.

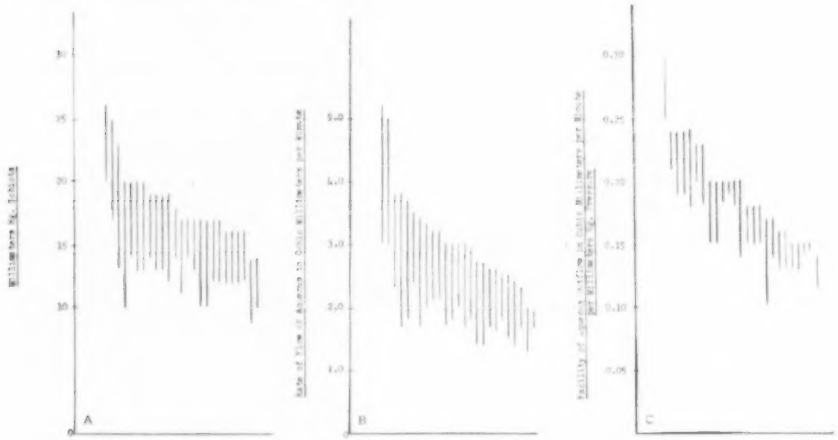

Fig. 2.—*A*, effect of intravenous injection of 100 cc. of 50% sorbitol on the intraocular pressure in 25 normal eyes. Each vertical line represents the change in intraocular pressure from just before to 30 minutes after the test in an individual eye.

B, effect of intravenous injection of 100 cc. of 50% sorbitol on the rate of flow of aqueous in 25 normal eyes. Each vertical line represents the change in rate of flow of aqueous from just before to 30 minutes after the test in an individual eye.

C, effect of intravenous injection of 100 cc. of 50% sorbitol on the facility of aqueous outflow in 25 normal eyes. Each vertical line represents the change in the facility of aqueous outflow from just before to 30 minutes after the test in an individual eye.

the experimental error. The total rate of aqueous outflow, which is another factor that can be calculated from tonography, was obtained from these experiments. A decrease in the total rate of aqueous outflow followed the injection of sorbitol, corresponding to the drop in the intraocular pressure. Furthermore, it was noticed that when the intraocular pressure resumed its original value, the rate of flow of aqueous also returned to its preinjection level, while all this time the facility of aqueous outflow remained approximately unchanged. Forty-eight eyes with various stages of chronic simple, open-angle glaucoma were used for this part of the study, the diseased stages varying from relatively early to far-advanced.

Table 1 presents a typical case in this group.

Mrs. A. W. was a patient with well-established bilateral chronic simple, open-angle glaucoma, whose tension had previously been adequately controlled with a miotic regime. At the beginning of the experiment the intraocular pressure was elevated in each eye. It dropped from 37 to 15 mm. in the right eye and from 30 to 15 mm. in the left eye in half an hour after the administration of 100 cc. of 50% sorbitol intravenously. During this time, the facility of aqueous outflow remained approximately unchanged, being about 0.13 cu. mm. per minute per millimeter Hg pressure in the right eye and 0.15 cu. mm. in the left eye. During the same time, the total rate of aqueous outflow decreased from 4.2 to 1.9 cu. mm. per minute in the right eye and from 3.8 to 1.9 cu. mm. in the left eye. Within the next hour and a half, the intraocular pressure slowly rose to the original level again, reaching 33 mm. in the right eye and 29 mm. in the left eye at the two-hour level. Two and one-half hours after the injection, both the tension and the rate of flow of aqueous of these eyes reached approximately the preinjection level.

Figure 2 shows the effect of intravenous injection of sorbitol on the aqueous humor dynamics in 25 normal eyes. Here, again, the greatest drop in the tension and rate of flow of aqueous took place 30 minutes after injection; within two hours both these values were back up to preinjection levels. Thus far the normal and the glaucomatous eyes showed similar responses to sorbitol. In the facility of aqueous

TABLE 2.—*Effect of Intravenous Injection of 100 Cc. of 50% Sorbitol on Facility of Aqueous Outflow, Total Rate of Flow, and Intraocular Pressure in Normal Eyes**

	O.D.†			O.S.†		
Time	C	K	I.O.P.	C	K	I.O.P.
8:00 a. m.	0.30	5.2	20	0.24	3.8	19
8:20 a. m.	100 cc. of 50% sorbitol injected intravenously					
8:55 a. m.	0.25	3.0	18	0.21	2.3	12
9:50 a. m.	....	...	17	....	...	17
10:10 a. m.	....	...	19	....	...	17

* Mr. F. B.

† C indicates cubic millimeters per minute per millimeter Hg pressure; K, cubic millimeters per minute, and I.O.P., millimeters Hg intraocular pressure.

outflow, however, the normal eyes showed some decrease, which was related to the decrease in tension and total rate of flow, followed by a subsequent rise in all three factors. In this respect, the normal eyes differed from the glaucomatous eyes, since the latter did not show changes in the facility of aqueous outflow following the sorbitol injection.

Table 2 illustrates the typical response of normal eyes to the intravenous administration of sorbitol. The intraocular pressure dropped in both eyes within half an hour, and at the same time the total rate of aqueous outflow also decreased; corresponding to this there was a decrease in the facility of aqueous outflow. Approximately two hours after the sorbitol administration the intraocular pressure was back to the preinjection level.

In the previous communication, the effect of the water-drinking test on glaucomatous eyes was reported to show an increase in the intraocular pressure, corresponding with an increase in the total rate of flow of aqueous following the ingestion of 1,000 cc. of water, while simultaneously the facility of aqueous outflow remained approximately the same. To study the effect of water ingestion on the normal eye as well, tonographic studies were performed on a group of normal subjects (25 eyes) both before and after the ingestion of 1,000 cc. of water. Figure 3 demonstrates that there was very little change in the intraocular pressure following

the ingestion of water, the rise in tension being from 1 to 4 mm. Hg. However, there was a simultaneous increase in the total rate of flow of aqueous and also an increase in the facility of aqueous outflow, as found by tonography. Table 3 shows a typical, normal patient's response to this test; after 1,000 cc. of water was drunk, on an empty stomach, the intraocular pressure changed only minimally, whereas, at the same time, there was a considerable increase in the rate of flow of aqueous through the eyes, the values changing from 2.4 to 3.6 cu. mm. per minute in the right eye and from 2.8 to 4.1 cu. mm. per minute in the left eye. Corresponding to this, the facility of aqueous outflow also increased from 0.19 to 0.24 cu. mm. and from 0.20 to 0.28 cu. mm. per minute per millimeter Hg pressure respectively.

It was reported in the previous communication that eyes with chronic simple glaucoma without medication showed considerable changes in intraocular pressure

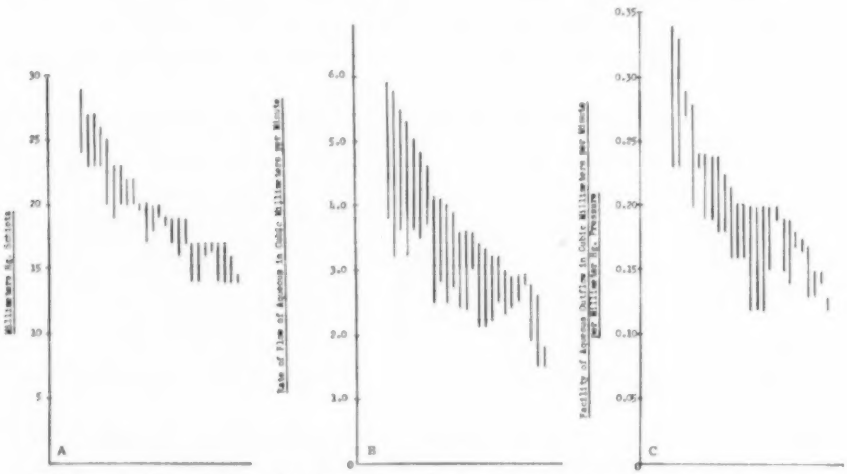

Fig. 3.—*A*, effect of water-drinking (1 liter of water in four minutes on fasting stomach) on the intraocular pressure in 25 normal eyes. Each vertical line represents the change in intraocular pressure from just before to 30 minutes after the test in an individual eye.

B, effect of water-drinking test (1 liter of water in four minutes on fasting stomach) on the rate of flow of aqueous in 25 normal eyes. Each vertical line represents the change in the rate of flow of aqueous from just before to 30 minutes after the test in an individual eye.

C, effect of water-drinking test (1 liter of water in four minutes on fasting stomach) on the facility of aqueous outflow in 25 normal eyes. Each vertical line represents the change in the facility of aqueous outflow from just before to 30 minutes after the test in an individual eye.

TABLE 3.—*Effect of Water-Drinking Test (1 Liter of Water on Fasting Stomach) on Facility of Aqueous Outflow, on Total Rate of Flow, and on the Intraocular Pressure in Normal Eyes*

	O.D.†			O.S.†		
Time	C	K	I.O.P.	C	K	I.O.P.
8:10 a. m.	0.19	2.4	14	0.20	2.8	16
8:20 a. m.	1,000 cc. of H_2O taken by mouth in 4 min.					
8:50 a. m.	0.24	3.6	17	0.28	4.1	17
9:30 a. m.	....	...	16	....	...	17
10:00 a. m.	....	...	17	....	...	16

* Mrs. H. M.

† C indicates cubic millimeters per minute per milliliter Hg pressure; K, cubic millimeters per minute, and I.O.P., millimeters Hg intraocular pressure.

during the course of the day, while the facility of aqueous outflow remained approximately the same. A detailed breakdown of results shows that of the 40 eyes with chronic simple glaucoma untreated and not operated on that were studied for spontaneous diurnal changes, 22 showed significant variations in tension and in the rate of

TABLE 4.—*Spontaneous Diurnal Changes in Total Rate of Aqueous Outflow and in Intraocular Pressure in Twenty-Two Eyes with Chronic Simple Glaucoma That Had Not Been Operated on and Had Had No Medication for Thirty-Six Hours Prior to This Examination*

Patient No.	Percent Change in K *	Change in I.O.P.†
1	55	18
4	100	22
5	36	13
6	105	21
7	86	18
10	44	14
11	33	15
13	58	15
14	67	13
20	59	16
24	33	15
25	88	14
26	65	15
27	31	17
28	103	25
29	69	16
31	67	18
33	75	22
34	33	14
35	41	21
36	67	17
38	40	14
Average	61%	17 mm. Hg

* K signifies the total rate of flow of aqueous and is expressed in the percent change during the day between the highest and the lowest value.

† I.O.P. shows the intraocular pressure, in millimeters Hg, and signifies the difference between the highest and the lowest value during the day.

TABLE 5.—*Spontaneous Diurnal Variations in Facility of Aqueous Outflow, in Total Rate of Flow, and in Intraocular Pressure in a Patient with Chronic Simple, Open-Angle Glaucoma in Both Eyes, Not Operated on and Without Miotic Medication for Thirty-Six Hours Prior to This Test*

Time	O.D.*			O.S.*		
	C	K	I.O.P.	C	K	I.O.P.
9:20 a. m.	0.07	3.0	50	0.08	2.9	41
11:50 a. m.	0.07	2.2	37	0.10	3.0	35
2:10 p. m.	0.07	1.9	32	0.08	1.8	20
5:00 p. m.	0.06	1.8	35	0.09	2.2	28

* C indicates cubic millimeters per minute per millimeter Hg pressure; K, cubic millimeters per minute, and I.O.P., millimeters Hg (Schiøtz).

flow of aqueous during the course of the day. Table 4 demonstrates that this change in the total rate of flow varied from 31% to 105%, with an average of 61%, while at the same time the intraocular pressure change varied from 13 to 25 mm. of mercury, with an average of 17 mm. of mercury during the course of the day.

Table 5 illustrates a typical case, taken from the previous study, that of Mr. A. W., a patient with chronic simple glaucoma in both eyes that had not been operated on and had been without miotics for 36 hours prior to this test. The facility of outflow remained approximately unchanged in both eyes throughout the day. The other two factors, however, varied considerably; as the intraocular pressure dropped, the rate of flow of aqueous decreased concurrently; and, vice versa, as the ocular tension rose, the rate of flow increased simultaneously during the course of the day.

COMMENT

Several interesting observations can be obtained from the above-recorded tonographic results. Raising the osmotic pressure of blood by injecting sorbitol intravenously resulted in a decreased rate of flow of aqueous, both in the normal and in the glaucomatous eyes. Concurrently, the intraocular pressure dropped, to a limited degree in normal eyes and somewhat more in eyes with chronic simple glaucoma. The facility of aqueous outflow also decreased in normal eyes, while it did not change in the glaucomatous eyes. Lowering the osmotic pressure of blood by the ingestion of water produced just the opposite effect. In this case, the rate of flow of aqueous and the ocular tension increased in both normal and glaucomatous eyes; the facility of aqueous outflow increased only in the normal eyes, while in the glaucomatous eyes it remained unchanged. The increased pressure is negligible in the normal eye, while it is of considerable magnitude in the eye with chronic simple, open-angle glaucoma.

It is evident that the variations in the osmotic pressure of blood affect the total rate of flow in both normal and glaucomatous eyes, as measured by tonography, the hypertonic solutions causing a decrease in the flow of aqueous and the hypotonic solutions resulting in an increase in the rate of flow. Furthermore, it becomes apparent that these variations are temporary; their maximal effect lasts only half an hour to one hour, and by the end of the second or third hour the status of the intraocular pressure and that of aqueous humor dynamics are back to normal or pretest values again. As far as the resistance to the outflow of aqueous is concerned, however, there is considerable difference between the glaucomatous and the normal eye as measured by tonography. In eyes with chronic simple, open-angle type glaucoma, the facility of aqueous outflow does not seem to be markedly influenced by changes in osmotic pressure of the blood. In the normal eye, on the other hand, there is some change in the facility of aqueous outflow following these osmotic changes in the blood. Thus, the facility of aqueous outflow, which is a measure of resistance to the outflow, appears to be an elastic, changeable factor in normal eyes; it can increase or decrease, depending upon the drainage load that is put upon the eye.

The investigations of Duke-Elder,[5] Kinsey,[6] and Goldmann,[10] in the last few years, have indicated that the intraocular pressure is a factor of the resistance to the aqueous outflow and the toal rate of flow. This has been shown clinically by Grant's ¶ tonography and by a combination of Goldmann's [10] fluorescein test and the measurement of the episcleral venous pressure and outflow pressure. Thus, it is not surprising that if the resistance to the outflow is impaired, and this impairment is of

¶ References 7 and 8.

a constant nature, the changes in the rate of flow of aqueous into the eye will have a considerable influence on the height of the intraocular pressure in that eye. The present investigation indicates that such appears to be the situation in eyes with chronic simple glaucoma not operated on and untreated. That is to say, the resistance to the outflow of aqueous as measured by tonography seems to be a fairly constant factor; it is not influenced by diurnal changes in aqueous humor dynamics and is not affected by artificially induced changes in the osmotic pressure of the blood. However, these osmotic pressure variations in the blood will cause changes in the rate of flow of aqueous into the eye, which, in turn, will result in variations of the intraocular pressure.

Reexamination of the results of the previous study showed that in eyes with chronic simple glaucoma when the spontaneous diurnal pressure variations were considerable, the rate of flow of aqueous also was changing significantly. Thus, there might be a relationship between these two factors in this type of primary glaucoma.

The spontaneous changes in intraocular pressure that exist to a limited extent in normal eyes and that take place to a considerable degree in glaucomatous eyes have excited the imagination and interest of research workers for a considerable period of time. Various factors that might cause these diurnal changes in intraocular pressure have been considered and discussed. The early investigations upon this aspect of glaucoma research were extensively discussed by von Sallmann [20] in 1930, who presented further evidence that changes in the tone of the extraocular muscles, that is, the movements of the eye during the day, have some bearing on these diurnal pressure variations. Since then, many other factors have been discussed and mentioned as a probable cause of the phasic variations in ocular tension. In recent years this problem was discussed by Duke-Elder [21] in the 1951 Proctor Lecture, in which he advocated mainly a vascular factor as the causative agent in the diurnal pressure variations in glaucoma.

It seems possible that several factors play a role; for instance, some people have advocated that the diurnal pressure changes in glaucoma are due to a redistribution of the blood following postural changes during the day and the night. Others have suggested that the movements of the pupil affect the intraocular pressure; the action of light on the ocular capillaries also has been mentioned as a probable causative factor. The massage of the eye by muscular movements during the course of the day, as postulated by von Sallmann, has been considered; the vascular factors have been well described by Duke-Elder. The present investigation suggests that osmotic changes of the blood might also play a part in these diurnal pressure variations in glaucoma. It appears that during the course of the day there are some spontaneous changes in the rate of flow of aqueous through the eye and that these variations in the rate of flow are concurrent with the tension changes. It was demonstrated, also, that various artificially induced changes in the osmotic pressure of the blood have, in turn, an effect on the rate of flow of aqueous through the eye. Therefore, there seems to be at least some circumstantial evidence to indicate that osmotic changes in the blood may play a part in these spontaneous diurnal pressure changes in glaucoma. Food and water intake, exercise, and loss of fluids through perspiration will cause periods of relative hemodilution and hemoconcentration throughout the day. Such diurnal changes in the osmotic pressure of the blood might be sufficient to

cause variations in the ocular tension. These results do not necessarily mean that the pressure changes are caused by the osmotic changes; they only imply that this might be the case.

The findings in the present investigation concerning the effect of sorbitol differ somewhat from the previous results of Bellows.# He found the pressure drop to be effective only a few hours following the injection and according to his results, the pressure remained lowered for several hours, or even a day or more, following the administration of the hypertonic solution. According to the results of the present study, the peak pressure drop occurred within half an hour following the intravenous injection of sorbitol and the intraocular pressure was back to approximately preinjection levels within two or three hours. The reports of other investigators employing sorbitol intravenously indicate that the maximum osmotic effect takes place rapidly after the injection of this material. Schwartz and Elman,[22] for instance, studying the effect of sorbitol on the cerebrospinal fluid pressure and the urine output, demonstrated that in dogs the peak in diuresis and the pressure reduction occurred within one-half hour following the intravenous administration of this solution; within two hours the cerebrospinal fluid pressure and the rate of urine output were back to normal. West and Burget [23] studied the effect of sorbitol on diuresis in the dog and noted marked action within 15 to 20 minutes following its intravenous injection. Wick and Drury,[24] employing C^{14}-labeled sorbitol injected intravenously into rabbits, demonstrated that sorbitol has approximately the same distribution space as dextrose; it diffuses into extracellular body fluids, i. e., approximately into 25% of body weight. They also showed that this diffusion of sorbitol into the extracellular body fluids is rapid, occurring within the first hour following the injection.

The above-cited physiological studies indicate that sorbitol rapidly diffuses into the extracellular body fluids after intravenous injection and that, therefore, its osmotic effect is short-lived. It is also rapidly excreted by the kidneys, most of it being eliminated within the first few hours following injection. Therefore, theoretically, one would not expect the osmotic effect to remain for several hours following the injection. On the contrary, the osmotic response should be almost immediate, commencing within a few minutes and reaching a peak in approximately half an hour following injection. Furthermore, the osmotic effect on the flow of water in the eye is also expected to be a brief one, because Kinsey and associates [25] demonstrated that water diffuses rapidly into and out of the eye. Thus, one would expect the osmotic effect of sorbitol following intravenous injection into man to be short-lived, reaching its peak in approximately half an hour and then subsiding within the next hour or two. The present investigation demonstrates that both in normal and in glaucomatous eyes the response on aqueous humor dynamics following the injection of this hypertonic agent was of short duration only.

Therefore, from a practical point of view, the use of sorbitol is limited in the treatment of glaucoma. The marked pressure-reducing effect occurs relatively soon after the injection of this material, but it is short-lived, lasting only about an hour. In this investigation, sorbitol was used to study the mechanism of primary glaucoma; it is not considered to be a diagnostic or therapeutic procedure in glaucoma.

References 16 and 17.

SUMMARY

Tonographic measurements indicated that variations in the osmotic pressure of blood affect the total rate of flow of aqueous in both normal and glaucomatous eyes, hypertonic solutions causing a decrease in flow, while hypotonic solutions result in an increase in flow.

The facility of aqueous outflow of the glaucomatous eyes was not influenced appreciably by the osmotic pressure variations of the blood. In normal eyes, however, there was a noticeable change in the facility of aqueous outflow following these osmotic changes in the blood.

Spontaneous diurnal pressure variations in eyes with chronic simple, open-angle glaucoma neither treated nor operated on seemed to be related to simultaneous changes in the rate of flow of the aqueous humor.

635 W. 165th St.

Sir Stewart Duke-Elder gave helpful advice in my work.

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DIAGNOSTIC VALUE OF FOVEAL ENTOPTIC PHENOMENA IN GLAUCOMA

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THE AIM of this investigation was to test the diagnostic value, in glaucoma, of two foveal entoptic phenomena, the Maxwell spot and the Haidinger brushes.

Maxwell's spot, so named for James Clerk Maxwell (1856), was long considered to be produced by a local depression of the effective retinal illumination through the strong absorption of blue light in the macular pigment. Walls and Mathews,[1] after reviewing and accepting earlier evidence given by other authors, came to the conclusion that it is caused by a local nonuniform distribution of the chromatic receptors in the fovea, the receptor-type distribution pattern (RDP). However, in the present report the name with the longer tradition has been retained and will be abbreviated MS herein.

Little is known about the perceptibility of the MS in pathological cases. It was studied in color-defectives by Ahlenstiel.[2] When looking toward the overcast sky (color temperature about 6500° K, the color defectives did not perceive the MS like color-normals but saw a lighter spot through a red filter and a darker spot through a crystal violet filter. Ahlensteil, with his method, established that more color-defectives than normals perceived the MS. Walls and Mathews, whose method was used also in the experiments reported below, found that all but one of 64 color-normal persons saw the MS, without exception describing it as being red in hue. Protanoids (protanomals and protanopes) perceived the MS as a local darkening of a pale blue background or as a blue spot. Most deuteranoids (deuteranomals and deuteranopes) saw no trace of the phenomenon. Two totally color-blind subjects did not perceive it.

The entoptic phenomenon named for W. K. von Haidinger (1844) appears as a spindle subtending 4 to 5 degrees of arc. It is visible, owing to the absorption of polarized light in the doubly refracting, slightly yellowish substance of Henle's fibers, which constitute a kind of radial analyzer in the fovea (von Tschermak-Seysenegg [3]). The testing of patients for Haidinger's brushes was recently emphasized by Goldschmidt.[4] Among others, he mentions a patient with a unilateral glaucomatous atrophy of the optic nerve who saw the phenomenon with the affected eye. Goldschmidt supposes that the recognition of Haidinger's brushes would be disturbed in glaucoma as soon as the papillomacular bundle is involved or there is a secondary degeneration of Henle's layer or both. He emphasizes that involvement of the macula which has been overlooked in an ophthalmoscopic examination may be revealed by this test. According to Boehm,[5] a protanope and a deuteranope

The Knapp Memorial Foundation, Institute of Ophthalmology, Columbia University, New York, granted a stipend which made it possible to carry out these studies.

perceived Haidinger's brushes like normals; a tritanomal saw them slightly differently from normals, and three totally color-blind persons with the macular pigmentation nearly lacking did not perceive them.

METHOD

Maxwell's Spot.—The MS was studied by essentially the method of Walls and Mathews in order to get comparable results. The examinee looked toward an extensive light source alternately through a purplish Wratten gelatin filter No. 2389 and through a Wratten neutral density filter (No. 96) of density 1.5, so that the light looked about equally bright through the two filters. The light source was similar to the viewing box used by Walls and Mathews, consisting of a 100-watt bulb in an aluminum reflector with a flashed opal glass 10 by 29 cm. in front. The color temperature of this arrangement is near to that of CIE Illuminant A; this is important to maintain, since the appearance of the MS is dependent upon the illuminant used. Both filters were mounted in a wooden frame and could be moved along a slide bar to the right and to the left in front of a black cardboard with an aperture of 2 cm. diameter.

When one looks through the aperture and through the No. 2389 filter, an uncontoured spot of a vivid red color can be seen at once. The color becomes still more vivid during three to four seconds' observation. In normals the MS is always described by a color designating a reddish hue: lighter or deeper red-purple, pink, or orchid; the background is called purple, lavender, orchid, violet, or blue. The spot is round or slightly oval, sometimes with radiate edges; some persons see an outer ring, separated from it by a lighter clearing. Many persons observe a small, lighter or darker central spot.

After five seconds of observation the MS begins to fade. It disappears entirely after 15 to 20 seconds. If now the purplish filter is replaced by the neutral filter, a greenish "after-image" of the MS appears on a yellowish background. This after-image, explained by Walls and Mathews as "the consequence of differential adaptation of the receptor types," becomes visible without any noticeable latency period and does not show any periodicity. Its appearance depends on the conditions of observation. The after-image is optimal after a preliminary observation of the primary image for 10 to 20 seconds. If the image is interrupted after a few seconds only by shifting to the neutral filter, the after-image is yellowish, pale, and hardly perceptible and fades very fast. Whereas on a low-luminance background the MS is seen with difficulty, the after-image is more striking, since it appears as a light, slightly bluish-green spot on a greenish-yellow background. If the filters are alternated with a frequency of about 2 per second, the MS becomes darker but more distinct in its details and does not fade; but when the alternation is stopped, the MS or the after-image (if stopped on the neutral filter) disappears very soon. The visibility of the MS can be improved by blinking, which is a known means of preventing local adaptation. The MS appears most colorful at the first test. When the test is repeated after a short break, it does not develop so well. Physical fatigue or bad health is unfavorable for observing the MS.

The patients were instructed precisely before the test in order to get a decisive answer from a first short observation. If the MS could not be seen on the first test, then, after a break, a second test was made by alternating filters continuously. A negative result on one eye was more reliable if the other eye perceived the phenomenon.

The size of the MS was measured by placing successively Cellophane sheets, with black circles of different diameters and with a central point, in front of the viewing box. From a distance of 1.5 meters, the patient chose the circle that fitted best the MS. During these measurements the filters were alternated frequently in order to avoid fading of the phenomenon. According to Walls and Mathews, a normal MS on the average subtends 3 degrees of arc; the central spot, ½ degree of arc.

The visibility of the MS is a function of the retinal illuminance. The testing of glaucoma patients was complicated by the fact that most of them had small pupils following pilocarpine treatment. An artificial aperture smaller than the natural pupil of any subject, glaucomatous or "control," would have put all subjects on an equal footing with respect to the retinal

illuminance. But this kind of common denominator could not be applied, since most patients had difficulty in observing through small apertures. Therefore the patients observed through an aperture of 2 cm. diameter, and the luminance of the viewing box was adjusted to compensate for the small pupils of the glaucoma patients in order to bring the testing conditions into line with those used with normal, control subjects.

The normal range of retinal illuminance for low, moderate, and good visibility of the MS was established on five persons whose color vision was normal according to the Nagel anomaloscope (anomalous quotients 0.8 to 1.2; see below). The subjects looked through artificial pupils at three different luminances. The artificial pupils, of 0.5, 1.0, 1.5, and 2 mm. diameter, were positioned as near as possible to the eye of observer. When the subject was looking through the neutral filter, the luminance was made 17, 32, or 82 mL. either by approaching the bulb to the opal glass or by substituting an opal glass with a higher transparency. These procedures introduced unavoidable minor color temperature changes. The retinal illuminance corresponding to each luminance and each artificial pupil was calculated in trolands, using a formula modified by de Groot and Gebhardt [6]:

$$E \text{ (troland)} = 10\, r^2\, B\, (1 - 0.0425\, r^2 + 0.00067\, r^4)$$

where r is the radius of the pupil and B the luminance of the adapting field, in millilamberts. The expression within the parentheses is the correction for the Stiles-Crawford effect (for white light). The ranges of visibility of the MS, which is actually observed through the purple filter, are then indicated in terms of the retinal illuminance when seen through the neutral density filter, which has about the same white-light transmission as the former. Thus, a complicated correction of the Stiles-Crawford effect for a purplish color was avoided, and the desired information still obtained. The average diameters of a natural pupil belonging to each of the three adaptation luminances were calculated from a formula by de Groot and Gebhardt and found equal to 3.4, 3.2, and 2.8 mm. These values set a limit for the use of larger artificial pupils. When the subject had evaluated the visibility of the MS with each pupil and each external luminance, and the corresponding retinal illuminances had all been calculated, it became possible to establish the following ranges of perceptibility of the MS in normals:

Visibility of MS	Trolands
Low	Up to about 20
Moderate	20 to 80
Good	Above 80

A low visibility was recorded if the MS was not seen at once. At a retinal illuminance of, e. g., 10 trolands the MS was not seen but the after-image was slightly visible. The MS, however, appeared as soon as the two filters were alternated. Within the range of moderate visibility the MS was perceived as a dark-red spot, suggesting a smudge in the filter; the after-image was clearly recognizable. Alternating the filters improved the visibility of the MS markedly. In the zone of good visibility the MS was seen at once in its vivid red color. The range of good visibility obviously has an upper limit, since an increasing luminance deteriorates the discrimination of the MS. This limit, however, was not established.

Since artificial pupils do not reproduce exactly the conditions of observing with a constricted natural pupil, tests were performed by instilling pilocarpine into the conjunctival sac of a normal eye: a test with one drop of 2% pilocarpine hydrochloride and a test with two drops of 2% pilocarpine hydrochloride in the left eye (Subject I. S., anomalous quotient 1.08). The results were recorded only when the pupils were rigid. The limits of ranges are of about the same magnitude with natural and with artificial pupils. In an area of 100 trolands and above there was good visibility of the MS in both conditions. Tests with 2% pilocarpine hydrochloride were not continued, however, because of vitreous opacities occurring as an after-effect in the subject's eye.

The established ranges serve as a basis from which to obtain results comparable with those found in normals, by using sufficient "supernormal" retinal illuminance to compensate for a pilocarpinized pupil. Testing was done in the range of 200 to 400 trolands.

Haidinger's Brushes.—This phenomenon, herein abbreviated HBs, can be easily perceived when looking through a rotating polarization filter and a blue filter toward a bright light source, as suggested by Boehm [5] and as done by Goldschmidt [4] with a handy apparatus. The HBs remind one of a rotating propeller. In the present experiments a neutral, linearly polarizing filter was fastened on the outer ring of a miniature ball bearing. When looking through its axial aperture of 1.5 cm. diameter toward a viewing box with a ground glass in front of a 100-watt bulb, the examinee viewed through the polarization filter and through a blue filter (Schott-BG 12, 2 mm. thick) fastened on the other side of this aperture. The polarization filter was turned by pushing the outer ring of the ball bearing. The optimal frequency was about 2 per second (a frequency as low as 5 per second markedly lessened the visibility of the HBs). The statement of the patient could be checked conveniently during the observation by changing the direction of the rotation. The visibility of the HBs depends on the retinal illuminance of the observer, among other factors. Two luminances were used: 4.0 and 6.7 mL. measured by a Macbeth Illuminometer when the examinee was viewing through both filters. A low visibility of HBs was found in five normals at 2.5 trolands, and a range of good visibility, between 4 and 170 trolands.* With higher retinal illuminances the HBs becomes faintly visible. A normal pupil, narrowed by pilocarpine to a diameter of 1.2 mm., did not affect the perceptibility of the HBs at the two luminances used. Testing was done in the range of 25 to 120 trolands. Untrained persons have less difficulty in seeing the HBs than the MS, obviously because the HBs attract the attention by their rotation and by their brightness contrast. The HBs can be observed continuously, since local adaptation is avoided by changing the illumination of the retina in rotating the polarization filter. They disappear shortly, of course, after the rotation is stopped. This test was used as a pass-or-fail test, not requiring observation of details.

Both phenomena are seen best on a level of medium bright adaptation of the eye. Therefore, the tests were performed in a laboratory with the ceiling lamp on. The patients faced a wall of about 4 mL. luminance.

The reports of Ahlenstiel and of Walls and Mathews show that there is a relation between the visibility of the MS and color vision. Therefore, the color vision was tested in most patients, especially in those reporting peculiarities of the MS. It had to be considered also whether the effect of pilocarpine on color vision would affect the visibility of the MS, nearly all patients being on chronic pilocarpine medication. From a report of Kravkov,[7] we know that pilocarpine increases the sensitivity to orange-red and decreases that to green and blue. In order to investigate whether this effect, established by threshold measurements, can be detected also with the Nagel anomaloscope (exit pupil 0.6 mm. diameter), a normal person (I. S.) performed 10 matches before and 10 after instillation of pilocarpine into the conjunctival sac of the left eye. One drop of 1% pilocarpine hydrochloride did not produce any effect on the Rayleigh equation (red + green = yellow) after half an hour, but two drops of 2% pilocarpine lowered the average of 10 mixture readings from 42.1 to 36.6 after half an hour, a finding which may indicate a decrease of green sensitivity (or an increase of red sensitivity) of significant magnitude (although not large enough to remove the subject from the "normal" category). One hour after the instillation the average reading returned to its initial value of 42.1. Although this experiment was very successful, not everyone would wish to repeat it, since, besides the narrowing of the pupil to a diameter of 1.2 mm. as an after-effect, there appeared a very unpleasant, long-lasting vitreous discontinuity. Therefore no more pilocarpine tests were performed.

Since fields for colors were not determined (this being too wearisome a procedure for the patients), they could only be deduced from those for white objects. Color isopters in many glaucoma patients remain parallel to the white fields, if constricted, contrary to the findings with primary optic atrophy, but in some glaucoma patients they are disproportionately narrower (Lauber [8]). As shown by Ferree, Rand, and Sloan,[9] normal pupils narrowed by pilocarpine do not affect field limits for white markedly, but contract the color fields for red and blue. These authors found two persons whose limits for red were widened by pilocarpine, whereas those for blue were narrowed, which results agree with those of Kravkov mentioned above. As follows from the preceding, it is a vague procedure to deduce color fields from fields for white objects. However, it might be safe to conclude from a visible MS that the color fields for a red target must be larger than 3 degrees of arc.

* The Stiles-Crawford effect was not considered.

It would have been desirable further to test the macular pigmentation on these patients. This could not be done for lack of an appropriate simple subjective method, and also because observation of the fundus in red-free light would have required an enlargement of the pupils.

All subjects were glaucoma patients of the Institute of Ophthalmology of the Presbyterian Hospital. Most of them were studied during the course of their treatment.

RESULTS

Many patients had difficulty in seeing the MS in a first test, since they were not trained in observing optical phenomena. Some evidently suppressed the perception and/or report of a spot, fearing it to be an unfavorable symptom of their disease. Therefore, if deviations were found, a second test was performed.

A. Foveal Entoptic Phenomena Perceived.—The MS was seen by 45 patients, with the following distribution:

	No.
Clinical diagnosis suspect, among them some with no evidence of glaucoma	9
Secondary glaucoma suspected	3
Secondary glaucoma	2
Secondary glaucoma O.D., chronic narrow-angle glaucoma O.S.	1
Early simple glaucoma	4
Chronic simple glaucoma	14
Chronic narrow-angle glaucoma (including 5 of Table 2)	8
Chronic wide-angle glaucoma O.D., chronic narrow-angle glaucoma O.S.	1
Acute congestive narrow-angle glaucoma	2
Chronic congestive narrow-angle glaucoma	1

Sixteen of these patients with different forms of glaucoma were tested with HBs and could perceive them. The results with five patients of this group showing some peculiarities are given in Table 1.

The investigations on the group of 45 patients suggest the following conclusions:

1. The MS and the HBs can be seen by patients with different forms of glaucoma, as well as by patients with no evidence of glaucoma.

2. Their visibility is independent of visual acuity to a large degree: A patient with a visual acuity of 20/200 (with correction) and an aphakic patient without correction could perceive them.

3. Some of the patients had marked constriction of fields. However, the fixation points were free. It is remarkable that Patients 4 and 5 of Table 1 perceived the MS, although their whole residual fields were as small as an MS often is. That such patients perceive the HBs may be less astonishing, since it is imaginable that the rotation is visible if there is only an island of the doubly refracting substance left.

4. About one-half the patients had normal fundi; the other half showed diverse grades of affection—beginning cupping of discs, especially on the upper margin, or beginning atrophy. Case 5 of Table 1 is an exception, showing deep cupping.

5. Most patients of this group had normal color vision. Some persons were suspected of a beginning color vision defect (passing one test but failing another).

It has to be taken into consideration that the results on testing color vision of patients might be affected not only by therapy but also by factors not primarily affecting the color apparatus, namely, (*a*) lack of training, (*b*) decreased transparency and increased yellowishness of the lens, (*c*) low visual acuity, due to a

pathological process or to therapy affecting refraction, and (*d*) narrow pupils, causing reduced retinal illumination (and perhaps chromatic diffraction phenomena). The last factor is particularly important.

In the parafovea, the upper limit of the Purkinje phenomenon is found on a retinal illuminance of 40 to 50 trolands. It is obvious that such a condition would affect the result on color plate tests. The effect of luminance on the perceptibility of chromatic differences was studied recently by Brown.[10] Down to about 1.08 mL. (corresponding to 50 trolands) it remained constant. At lower luminances, color discrimination became poor; a normal observer appeared tritanomalous. The retinal

TABLE 1.—*Glaucoma Patients Perceiving Entoptic Phenomena*

No.		1	2	3		4	5
Name		Mrs. S.	Mr. H.	Mrs. C.		Mr. F.	Mrs. San.
Age, yr.		65	67	76		48	59
Form of glaucoma		Chronic narrow-angle	Chronic simple	Chronic simple		Chronic simple	Chronic simple
Eye		O. D.	O. D.	O. D.	O. S.	O. S.	O. D.
Pupil diameter, mm.		2.5, op.	1, rigid	1.5, rigid	1.5, rigid	1, op.	1.5, rigid
Visual acuity		20/25–2 c. c.	20/40–1 c. c.	20/200 c. c.	20/200 c. c.	20/400 s. c.	20/50+2 c. c.
Fundus; discs		No cupping	Obviously normal	Normal	Normal	Not seen	Deep cupping; arteriosclerosis
Central fields, in degrees (Illum. 10-ft.-c.)	nasal	21	22	24	21	1	2
	temporal*	11	18	11	11	8	2
	superior	14	17	22	2	3	2
	inferior	22	23	25	22	4	2
White object, mm./distance, mm.		2/1000	2/1000	5/1000	5/1000	2/1000	5/1000
Ishihara plates, total no. failed		1	12	7	13	4	20
H-R-R charts, nos. failed	illumination	1, 2, 3, 16, 18	1-10, 18	2-10, 18	2, 3, 5, 6, 18	1-6, 8, 9 15-18	....
	30 ft.-c.	2, 18	1-7	1-3, 5, 6 18		1-6, 8 15-18	1-7, 10, 13 15, 17
	60 ft.-c.						
Nagel anomaloscope	Anomalous quotient	1.8	1.15	.....	.....	.....	0.89
	Matching range, log units	0.222	0.079	.....	.....	.....	0.154
Bausch & Lomb anomaloscope, range		.....	.....	2 red-4 green	1 red-2 green	3 red-3 green	.....
Maxwell's spot:							
Primary image		Light red	Light red	Red	Red	Pink	Red
Background		Reddish	Purple	Cerise	Cerise	Violet	Purple
After-image		Greenish	Green	Light	Light	Greenish	Green
Background		White	Yellow	Yellow	Yellow	Yellow	Yellow
Haidinger's brushes		+†	+	+	+	+	+

* Fields on the temporal side of the blind spot are not considered, being of no interest for the topic of this report.

† + means seen.

illuminance produced by charts illuminated by the customary 30 ft.-c. on a patient with a pupil of 1 mm. diameter would be reduced to 36 trolands (assuming an average reflectance of plates of 0.45, and, therefore, a luminance of 14.6 mL.). This value is far below the minimum required in routine plate testing (20 ft.-c., corresponding to 250 trolands) and is also below the limit of the Purkinje phenomenon, mentioned above, and the critical value found by Brown for a safe color discrimination.

Since it is difficult to eliminate all secondary factors to establish how much of any apparent abnormality is actually due to a deterioration of color vision, the diagnosis of an acquired color vision defect in glaucoma patients should be made with caution.

The color vision of the patients was examined with several tests, with the instructions carefully followed. Of 36 patients tested with Ishihara plates (ninth edition), 21 plates being used, 9 persons failed, if 8 plates (40%) or more plates misread means failed, misinterpreting, respectively, 8, 10, 11, 12 (3 persons), 13, and 20 (2 persons) plates. The missed plates were not numerous with the exception of those of the two last persons. One of these two was aphakic, with a visual acuity of 20/50 with correction; the other was Patient 5 of Table 1, Mrs. San., who was an exception in several respects. She named the colors of single dots correctly but was not able to combine them into digits (field constriction[?]). The mistakes made by the patients on the Ishihara charts were different from those made by persons with congenital color deficiencies, since the "concealed" digits were no better recognized than the ordinary numbers. The mistakes mostly pertained to charts with low chromas. Patient 3 of Table 1 saw the numbers of deuteranoids better than those of protanoids. The other patients could not be classified as to type in terms of the regular classes of red-green defectives.

A few persons were tested with the Hardy-Rand-Rittler charts, which are in an experimental stage but already have proved to be very useful (Schmidt [11]). They contain three demonstration plates, a screening series (Nos. 1 to 5), and several series for classification, arranged in gradually increasing saturation: Plates 6 to 10 indicate a mild, Plates 10 to 12 a medium, and Plates 13 and 14 a strong red-green defect; Plates 15 and 16 indicate a medium and Plates 17 and 18 a strong blue-yellow defect. Moreover, they enable a classification of the type. The results of those persons making numerous mistakes are shown in Table 1. Except for Patient 5, none failed plates of the groups indicating strong red-green defect. None could be classified as to type. The five persons of Table 1 apparently have a strong blue-yellow defect. However, two of them failed only the last plate (No. 18), which might be a failure of the plate rather than a failure of the patient. Doubling the illumination improved the score of Patients 1 and 2 markedly.

Patients 1 to 4 were tested with the Stilling plates Nos. 32 to 35 (20th edition), designed to detect blue-yellow defects, and failed them. On the Farnsworth Dichotomous test Patients 1 and 3 made displacements typical of a tritan, while Patient 5 passed the test three times. This test does not demand any skill in integration.

The red-green vision was further checked † by the Nagel anomaloscope, which has an exit pupil of 0.6 mm. diameter and therefore allows testing of pilocarpinized subjects and normal controls under conditions of equal retinal illuminance. The test field has a size of 2 degrees 10 minutes. The subject's performance can be indicated directly in scale units of the dial for the red-green mixture, but can be determined better by computing an anomalous quotient obtained by dividing the ratio of green to red required by the subject by the ratio of green to red for the average normal subject. The normal range of these quotients is 0.6 to 1.5. A low quotient signifies that more red is required, a high quotient that more green is required, in the mixture. The range of quotients in protanomalous subjects is 0.01 to 0.4; that of deuteranomalous subjects is 2.0 up to about 10.0. An enlarged range of acceptable mixtures indicates color deficiency, even if the average match is normal. Such a defect is called color amblyopia if an abnormal enlargement remains after neutral

† No spectral apparatus for testing blue-yellow vision was available.

adaptation, color asthenopia if it disappears after neutral adaptation. If the two extreme mixtures which a subject is able to accept are designated by the logarithms of anomalous quotients, the individual matching range can be computed from the difference of the quotients in log units. A normal range does not extend more than 0.245 log unit. An enlarged range of readings for the yellow stimulus, matching the red-green mixture, indicates poor intensity discrimination. Since most patients had difficulty in handling the anomaloscope, the experimenter set the dials herself.

Patients of this group were normal on the Nagel anomaloscope (insofar as they could be tested with it) even if they failed chart tests (Table 1). The man with the aphakia who failed 20 Ishihara plates had difficulty centering his eye at the anomaloscope. He named correctly 48 chips of Ostwald colored paper (24 hues, each presented in two different value-chroma combinations). Two patients, 3 and 4 of Table 1, were not able to find the aperture of the Nagel anomaloscope and were tested on the Bausch & Lomb anomaloscope.[12] In this apparatus the color stimuli are produced by filters and the field is observed with a free pupil. The normal range is about one red to one green. The averages for both persons were normal. Considering their narrow pupils, their matching ranges may also be normal.

It is difficult to decide whether the five persons of Table 1 have normal color vision or not. If we apply the rule that color vision should be called normal if a majority of tests are "normal" (and consider the secondary factors which may cause deterioration of the scores), then Patient 1 has normal color vision, but a rather high anomalous quotient, characterizing her as a borderline case. Patient 2 has normal color vision. Patient 3 may have a mild color amblyopia of the right eye; the left eye is probably normal. Patient 4 may have a mild color amblyopia and a blue-yellow defect. It is amazing that he passed the Ishihara charts. Patient 5 is normal on the Nagel anomaloscope and on the Farnsworth Dichotomous test, but for some reason (field defects or inability to integrate pattern [?]) she shows a red-green and also a blue-yellow defect on chart tests.

B. Modifications of Maxwell's Spot.—Some modifications of the MS concerning size, color, or visibility of image or after-image were reported.

Modification of Size: A patient with chronic simple glaucoma (Mrs. R., No. 1, Table 2) reported for her left eye a MS of 35 minutes of arc. The HBs were perceived. The disc in the left eye had a less extensive glaucomatous cupping than that in the right. With the right eye the MS and HBs could not be seen. The color vision of the left eye was normal; the anomalous quotient was 0.9. The value of 35 minutes suggests that the patient observed a MS consisting only of the central spot. Walls and Mathews ‡ report a similar case, that of a man who saw the MS reduced to the central spot alone. His average match was shifted 1 to 2 scale units toward the red from the perfectly normal on the anomaloscope, which result agrees with that on Mrs. R.

Modification of Color: A patient of the first group, Mrs. Von K., aged 68, with chronic narrow-angle glaucoma, repeatedly reported a smaller and less intense MS on a bluer background for her left eye than for her right eye. There was no measurable difference, however, each MS subtending 2 degrees. The quotients on the

‡ Walls and Mathews,[1] p. 120.

Nagel anomaloscope were O.D. 1.0 and O.S. 0.84, confirming her subjective impression of a lower red sensitivity in her left eye. The right eye was on chronic treatment with pilocarpine (increasing its red sensitivity [?]); the left eye was not.

The observation of a normal person, I. S., her right eye having a quotient of 0.92, as compared with her left eye (quotient 1.08), supported the statement of Mrs. Von K.

Another patient, Mr. S., aged 64, with chronic glaucoma simplex, reported for each eye a dark MS, which was definitely not redder than the purple background. Through the neutral filter he saw a light cloud, which was definitely not greenish. Both phenomena were fast fading and were difficult to observe. The patient who used 2% pilocarpine twice a day in both eyes and was on chronic methantheline-(Banthine)-ephedrine therapy, had normal discs, except for conus myopicus, and did not show any other remarkable symptoms. The HBs were perceived with both eyes. The color vision was normal according to plate tests. On the Nagel anomaloscope he had low anomalous quotients: O.D., 0.66; O.S., 0.64, characterizing him as a borderline normal on the protanomalous side. It cannot be said whether this shift was congenital or was acquired through therapy or disease.

The cases reported are interesting in that already small variations of color sensitivity find a response in the appearance of the MS.

Two persons had elevated quotients on the Nagel anomaloscope, characterizing them as on the borderline of deuteranomaly. Patient 2 of Table 1 had quotients 1.8 O.D. and 1.45 O.S. She called the MS for her right eye a light red dot on a reddish background. Mrs. C., with a quotient of 1.75 for her right eye, did not observe any peculiarities of the MS. Both persons were on chronic pilocarpine (2%) treatment, three to four times a day. It is impossible to say whether the low green sensitivity was congenital or acquired by the therapy. Walls and Mathews § mention a person with a deuteranomalous setting on a filter anomaloscope who passed chart tests and observed a normal MS.

Deterioration of Visibility: Mr. D., 80, had chronic simple glaucoma. His right eye was amblyopic. For his left eye he reported a MS seen as a shadow or a dark ring on a blue background, in the after-image (senile macular affection [?]) a deeper color on a yellow background. The HBs were not perceived. Other symptoms: Pupil 2 mm., slightly active. Visual acuity 20/200 with correction. Lens, senile sclerosis. Disc, large cup, not very deep. Fields: nasal, 13 degrees; temporal, 17 degrees; superior, 7 degrees; inferior, 18 degrees (object 2/1000; 10 ft.-c.). Color vision: Ishihara test, 20 plates failed; Hardy-Rand-Rittler charts, under 60 ft.-c., Nos. 2, 5, 6, 12, failed. Farnsworth Dichotomous test, under 30 ft.-c., passed. Nagel anomaloscope: anomalous quotient 1.14; matching range 0.372 log unit. Diagnosis: defective red-green color vision; color amblyopia. In this case a deterioration of the visibility of the MS was found parallel with a deterioration of hue discrimination in the green-yellow-red spectral region.

In some cases the primary images were lacking but the after-images were perceived, a phenomenon which was mostly a result of insufficient retinal illuminance, and which was eliminated in retests (but not in the following case).

One case deserves special attention, that of Mrs. B., aged 67. She had chronic simple glaucoma and a series of other diseases, namely, anemia, cancer, rheumatoid

§ Walls and Mathews,[1] p. 146.

arthritis, and mild diabetes. She had difficulty in seeing the image with her right eye, whereas the after-image was visible. On a second test, two months later, there was no trace of the MS, beyond a slight shadow seen with alternating filters. With her left eye she saw the MS normally on a first test. On the second occasion only the after-image was visible. The HBs, tested on the second date only, were not seen with the right eye but were perceived with the left.

Other Symptoms: O. D.: pupil 2 mm.; visual acuity 20/60 without correction. Fundus: macular pigmentation in O.D. paler than in O.S. Disc: suspected of beginning cupping. Fields: nasal, 20 degrees; temporal, 11 degrees; superior, 13 degrees; inferior, 22 degrees (2/1000 object; 10 ft.-c.). Color Vision: Ishihara test, 18 plates failed; patient classified as a protanoid. Hardy-Rand-Rittler charts: Nos. 1-8, 11-16, 18 failed; type not identified. Bausch & Lomb anomaloscope: range, 4 red to 5 green; range tends to enlarge during observation. Diagnosis: color amblyopia.

O.S.: pupil 2 mm.; visual acuity 20/20. Fundus: pale macular pigmentation, but not as much as in O.D. (courtesy, Dr. R. L. Pfeiffer), Disc: beginning cup, no difference from O.D. Fields: nasal, 18 degrees; temporal, 9 degrees; superior, 12 degrees; inferior, 13 degrees. Color vision: Ishihara test, 16 plates failed. Hardy-Rand-Rittler charts: Nos. 1, 2, 15, 16, 18 failed. Nagel anomaloscope: anomalous quotient 1.1; matching range 0.192 log unit. Color vision therefore defective according to chart tests, but "Nagel-normal."

The remarkable result in this case is that the eye with the stronger color vision defect and with the slighter macular pigmentation did not perceive MS and HBs.

Some persons reported difficulty in seeing the after-image. That easily occurred if the MS was not observed long enough. It would be of interest to follow up this question more thoroughly in future tests, since after-image from colored objects can be lacking in advanced cases of glaucoma, as shown by Bock.[13]

C. Foveal Entoptic Phenomena Not Perceived.—If patients with absolute central scotomas are not counted, only six were unable to perceive the MS. The results on five of them, who could be investigated carefully, are shown in Table 2. All six patients were in an advanced stage of the disease, with marked field constrictions (Patient 5, O.S., to the fixation point), and all had defective color vision, in the eye with the MS lacking. According to chart tests, they should be called totally color-blind. Even the demonstration plates were hardly recognized, or were not recognized. On the Farnsworth Dichotomous test Patient 3 made displacements typical of red-green deficiency, while Patients 2 and 4 made tritanopic displacements. The Nagel test could be performed on only two patients, Nos. 2 and 4. The result was color amblyopia. The fundi of the six patients showed discs with marked glaucomatous cupping. It is of interest that Patient 1, with the eye having the less extensive cupping, perceived the MS and HBs. With the exception of the right eye of Patient 3, the eyes not perceiving the MS could not see the HBs. Patient 3, with her right eye almost totally color-blind and with nothing pathological in its fundus, perceived the HBs but not the MS. The visibility of the HBs is obviously independent of color vision, a suggestion which was confirmed by observations on a number of persons with congenital color vision defects (one protanope, two deuteranopes, and four deuteranomals), who all perceived the HBs.

TABLE 2.—*Glaucoma Patients Not Perceiving Entoptic Phenomena*

Patient no.	1		2		3		4		5	
Name	Mrs. R.		Mrs. A.		Mrs. Br.		Mrs. Al.		Mrs. T.	
Age, yr.	38		62		48		57		53	
Disease	Chronic simple glaucoma		Chronic simple glaucoma		Chronic narrow-angle glaucoma; late latent syphilis		Chronic simple glaucoma		Chronic narrow-angle glaucoma	
Eye	O. D.	O. S.	O. D.	O. S.	O. D.	O. S.	O. D.	O. S.	O. D.	O. S.
Pupil diameter, mm.	1; op.	Op.	1.5; rigid	1.5; rigid	1; rigid	1; rigid	1; rigid	1; rigid	4	2; slightly active
Visual acuity	Amblyopic	20/30 c. c.	20/50 s. c.	20/25 s. c.	20/25 s. c.	20/40 s. c.	20/25 c. c.	20/60 c. c.	20/25 s. c.	20/25 s. c.
Lens	Clear	Clear	Nucleus sclerotic	Nucleus sclerotic	Clear	Clear	Clear	Clear	Clear	Clear
Fundus, discs	Pale; extensive cupping	Less extensive cupping	Not seen, former record: Glaucomatous cupping OU.		No cupping	Deep cup; white disc	Marked cupping; atrophy	Marked cupping; atrophy	Normal	Pale; large cup
Central fields, degrees (illum. 10 ft.-c.) nasal	5	27	11	7	7	4	3	2	25	1
Central fields, degrees (illum. 10 ft.-c.) temporal*	8	11	10	12	11	6	3	7	11	1
Central fields, degrees (illum. 10 ft.-c.) superior	11	24	4	3	4	2	2	7	22	0
Central fields, degrees (illum. 10 ft.-c.) inferior	4	28	8	7	7	4	2	3	25	12
White object, mm./distance, mm.	HM/1000	5/1000	10/1000	10/1000	2/1000	2/1000	10/1000	Fingers	2/1000	2/1000
Ishihara plates, total no. failed	Not seen	2	20		20	21	20	Not seen	1	20
H-R-R charts, nos. failed (illum. 30 ft.-c.)	Not seen	0	1-18		1-18	1-18	1-18	Not seen	..	..
Nagel anomaloscope										
Average anomalous quotient	Testing impossible	0.9	Testing impossible		0— ∞	0.87	1.15	Testing impossible	..	..
Matching range, log units	—	0			∞	0.813	0.347			
Maxwell's spot†										
Primary image	—	Red (size 35')	—	—	—	—	—	—	Darker	—
Background	Purple	Purple	Purple	Purple	Blue	Blue	Purple or blue	Lavender	Purple	Purple?
After-image	—	Greenish-blue	—	—	—	—	—	—	Greenish	—
Background	Yellow	Yellow	Colorless	Colorless	White	White	Light blue or green	Green	Light	Tan
Haidinger's brushes†	—	+	—	—	+	—	—	—	Not tested	

* Fields on the temporal side of the blind spot are not considered, being of no interest for the topic of this report.
† — means not seen; +, seen.

COMMENT

The Maxwell spot and the Haidinger brushes disappear in an advanced stage of glaucoma only, in agreement with the fact that foveal functions are not impaired, or are scarcely impaired, until late in this disease.

The MS is a sensitive indicator of foveal color vision. If foveal color vision is normal and if central color fields are free in an area somewhat larger than its size, the MS can be perceived. From testing experience it can be concluded that everyone passing the Ishihara test can perceive the MS. If the hypothesis is correct that a MS is not seen if color fields are too narrow to allow it to be distinguished from its surround, it can be added that almost anyone who is "Nagel-normal" sees the MS, even if he fails chart tests. Individual variations of color sensitivity within the normal range were found, together with individually different appearances of the MS. A moderate decrease of the hue discrimination in the red-yellow-green spectral region affects the visibility of the MS to such a degree that it can become undistinguishable. It is not certain whether the blue-sensitive apparatus plays a role in the visibility of the MS, despite the fact that almost all persons not perceiving the MS had not only defective red-green vision, but also defective blue-yellow vision.

The HBs do not show a dependence on color vision, since they are perceived by persons with acquired and with congenital color deficiencies. Color-defective persons who do not perceive the HBs have at the same time visible fundus defects.

Most glaucoma patients who did not perceive foveal entoptic phenomena had extensive glaucomatous excavation of their discs. Obviously, the perception of foveal entoptic phenomena is preserved as long as the atrophy by pressure does not affect the papillomacular bundle (provided there is not a primary local process in the macula). The mechanism causing a disappearance of these phenomena may consist in a dysfunction or an interruption of the conducting sensory path in the optic nerve. Another possibility is a malproduction by secondary trophic lesions of the primary substances causing the phenomena, in the case of the MS the macula pigment (if this is its primary cause), in the case of the HBs the doubly refracting substance in Henle's layer.

The close relation between the visibility of the MS and the red-green aspect of color vision sustains the assumption that its lack can be associated with a defect in any level of the receptive or conducting system involved in the color vision process. In the case of Patient 3 (Table 2), with the MS lacking and with no fundus defects, a process in the conducting path or in the higher centers is very probable, since the patient has late latent syphilis with cerebral symptoms.

A disappearance of the HBs is obviously a symptom of a local primary or secondary macular process. At least in the glaucoma patients it was lacking only when there was a visible affection of the disc or of the macula.

It is of further interest to follow up whether the reported observations give a hint to the etiology of the MS. From the relation between the visibility of the MS and the color vision it is not possible to deduce whether the color-sensitive apparatus is primarily involved or is only mediating the visibility of the MS. The result on Mrs. B., with the MS not perceived in the eye with the paler macular pigmentation, speaks in favor of the pigment deficiency etiology of the MS. The fact that a dark-

red MS is observed with the eye having the lower red sensitivity can be interpreted in favor of either hypothesis. According to the concept valid until now, individual differences of color sensitivity within the range of normal red-green color vision (and also within each type of red-green color deficiency) are caused by differences in macular pigmentation. A decreased pigmentation would work like the removing of a yellowish filter from in front of the eye, allowing the fovea to be stimulated by more blue light from the purple filter, or by more green from the mixture field in the Nagel anomaloscope, and requiring more red to be added to the mixture to restore a match with the yellow. It is to be recalled that a case of Wieland [14] supports this idea: His patient had a very low macular pigment and showed on the Nagel anomaloscope an enlargement of the matching range toward the protanomalous side, which, when calculated as anomalous quotients, gave for O.D. 0.81 to 0.59 and for O.S. 1.1 to 0.46. However, it is conceivable also that the reported differences are caused by differences in the individual receptor-type distributor pattern. A less red and more purplish MS in one eye can be perceived if there are fewer redness receptors in the fovea and more blueness and greenness receptors than in the other eye.

The case with the MS together with a strong color vision defect and without a fundus affection does not allow of any conclusion. The MS may still be produced by the macular absorption but caused not to be perceived by a color vision defect from an affection of higher centers. A MS lacking simultaneously with the HBs indicates only that a local process in the eye is involved also. Conclusive evidence in favor of the Walls and Mathews hypothesis could be brought by persons perceiving the MS with a normal color vision and an extreme macular pigment deficiency. Such persons possibly could be found among albinos, who at the time of these experiments were not available.

A last question to be discussed is whether testing of entoptic phenomena is meaningful in glaucoma patients. These tests do not support an early recognition of the disease, but they complete, without doubt, the clinical picture, since the perception of entoptic phenomena is a positive index of foveal vision. They can give useful information where it is difficult to observe the fundus because of lack of transparency or inability to enlarge the pupils. If the MS is seen, foveal color vision is normal (or only slightly affected); therefore a testing for the MS can replace a color vision test, e. g., if a patient cannot be tested on the Nagel anomaloscope. A MS seen allows the conclusion that the central color fields are larger than 3 degrees. Presence of HBs signifies that the macular substance is not affected.

SUMMARY

The visibility of the Maxwell spot (MS) and of the Haidinger brushes (HBs) requires a certain amount of retinal illuminance. The normal range of the retinal illuminance for their visibility was established in order to test the patients on an even footing with normals, by adjusting the luminance of the light source to the pupils of the patients. Since it is known that congenital color deficiency affects visibility of the MS, the color vision of the patients was tested also. The results on color vision tests, if they are applied according to instructions, can be used only with caution, since the scores can be deteriorated by factors other than color vision, some of these being difficult to eliminate. A narrow pupil in some cases can be

blamed for an "apparent" blue-yellow defect established by chart tests. The Nagel anomaloscope allows the testing of all subjects at a constant retinal illuminance because of its small exit pupil. However, many elderly patients have difficulties in using this apparatus.

Forty-five of the 51 glaucoma patients with different degrees of the disease (some of them being only suspected of having glaucoma) perceived a normal MS, and those of this group investigated for HBs perceived these also. Therefore, these tests are not adapted for an early detection of this disease. Modifications observed on the MS are given in detail. They are apparently not specific for glaucoma. Only six patients who were with at least one eye in an advanced stage of the disease could not perceive the entoptic phenomena with this eye.

Most persons perceiving MS had normal discs; several showed a beginning cupping and atrophy. As a rule, those patients not perceiving MS had an extensive glaucomatous excavation of discs. Persons who see the MS pass the Nagel anomaloscope but do not necessarily pass the chart tests or other tests with pigment colors. Persons not seeing the MS fail tests with spectral colors and with pigment colors. An exception to this rule may be constituted by persons whose central color fields are smaller than would permit a perception of a separate MS but large enough to be tested on the Nagel anomaloscope. The acquired color vision defect which accompanies a lack of the MS is a low hue discrimination, showing on the Nagel anomaloscope as an enlargement of the matching range of mixtures.

The results on glaucoma patients suggest that the MS disappears not only on a visible fundus affection but also on a disturbance in a higher level of the nervous system involved in the color vision process. The observations on glaucoma patients cannot be employed to support either of the hypotheses concerning the etiology of the Maxwell spot.

The HBs are not dependent on color vision, since they can be seen by persons with acquired and congenital color deficiencies. Their disappearance is apparently linked with a primary or secondary affection of the macula.

Testing entoptic phenomena in glaucoma patients may be valuable in cases in which the fundus cannot be seen. Testing of the MS can be a substitute for testing foveal color vision. The advantage of the entoptic tests is their independence of refraction, of visual acuity, and of fixation (if measurement of size is not required); their short duration, and their simplicity of application.

Dr. W. S. Knighton gave me permission to carry out these tests on the patients of the Glaucoma Department of the Institute of Ophthalmology and allowed me to consult the hospital records of the patients.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

PLEXIFORM NEUROFIBROMA OF ORBIT AND LID WITH DEFECTS IN WALLS OF ORBIT AND INVOLVEMENT OF CENTRAL NERVOUS SYSTEM

PLEXIFORM neurofibroma of the orbit and lid with defects in the walls of the orbit and involvement of the central nervous system is a rare manifestation of von Recklinghausen's disease.

Peyton and Simmons,[1] in 1946, were able to collect 20 cases from the literature and presented 5 of their own.

REPORT OF CASE

H. M. R., an Arab boy 15 years old, was admitted to the Department of Ophthalmology of the American University of Beirut, in January, 1953, on account of a deformity of the left upper lid. The condition was congenital, noticed a few days after birth. The left upper lid gradually increased in size and became ptotic, covering the left eyeball completely (Fig. 1). There was no history of inflammatory attacks. The patient had not consulted any physician previously. He had no other complaints. His general health had always been very good.

Family History.—His parents are living and well. Two brothers and five sisters are all in good health. None has a similar deformity or any birthmarks. One brother and one sister have internal strabismus.

Physical Examination.—The patient appeared younger than his stated age and slightly under nourished, but was clear-minded and intelligent.

The parietal bosses were prominent, the left more than the right. The left eyelid was markedly hypertrophied, pendulous, and pigmented. This hypertrophy extended upward and outward beyond the orbital margin, involving the temporomaxillary region. The patient was unable to raise his left eyelid. The tumor was soft. Vermicular cords could be felt on pressure. When the eyelid was raised, the eyeball appeared to have normal size but was pushed downward and forward, with a marked inward deviation. No pulsations could be seen or felt. The cornea was clear. The pupil was of normal size, and it reacted to light and in accommodation. It dilated easily with homatropine. Ophthalmoscopic examination revealed clear media and a large pale, oval optic disc with deep physiological cupping. The rest of the fundus was normal. Tension was normal. Vision was counting fingers at 1 meter.

The right eye was normal; vision 20/20.

The general physical examination revealed numerous café au lait patches and spots all over the body. There were no cutaneous nodules. No other physical abnormality was found (Fig. 2).

Neurological examination was essentially negative. Perimetric examination showed a slight constriction of the left field of vision. The right field was normal.

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Roentgen-ray examination revealed a marked enlargement of the left orbit, with extensive destruction of the roof and posterior walls. The left maxillary sinus was compressed and hazy. The sella turcica was greatly widened, and the apex of the left petrous bone was partially destroyed, showing definite notching. There was no evidence of increased intracranial pressure. X-rays of the long bones showed no abnormality (Fig. 3).

A clinical diagnosis of neurofibroma of the left upper lid and orbit with intracranial involvement was made.

On Jan. 30, 1953, the patient was put under general ether anesthesia. A curved skin incision parallel to the lid margin and 2 cm. above it was made. Deep to the skin, strands of atrophic muscle tissue were seen and retracted. A white, soft tumor mass came into view. Further dissection revealed that the tumor had infiltrated the whole thickness of the upper eyelid and extended upward and outward beyond the orbital rim into the temporal region. A large

Fig. 1.—Pigmentation and marked hypertrophy of the left upper eyelid.

Fig. 2.—Picture taken five months postoperatively. Note the café au lait spots and patches over the trunk and extremities.

mass could also be felt above and behind the eyeball. The tumor within the eyelid was carefully dissected from the skin and conjunctiva. No definite line of demarcation being present, the dissection was not easy and not complete. The orbital growth, however, the size of an egg, could be freed from the surrounding orbital tissue and removed. The eyeball itself and the optic nerve were not invaded. Definite bony defects could be felt in the roof and posterior aspect of the orbit. There was free bleeding during the dissection. After removal of the growth an elliptical strip of skin and hypertrophic conjunctiva was removed from the lid, thus shortening it. The wound was closed with interrupted nonabsorbable surgical (silk) sutures. The postoperative course was uneventful. The patient was discharged on Feb. 13, two weeks after operation. The pathologist's report read as follows: "This is a pure tumor of nerve tissue. It consists of fibers running parallel, many of which have large bodies, which, when analyzed, are seen to be collections of mucoid material in the nerve cells (Fig. 4). It seems to me that the picture fits nicely with the diagnosis of von Recklinghausen's disease."

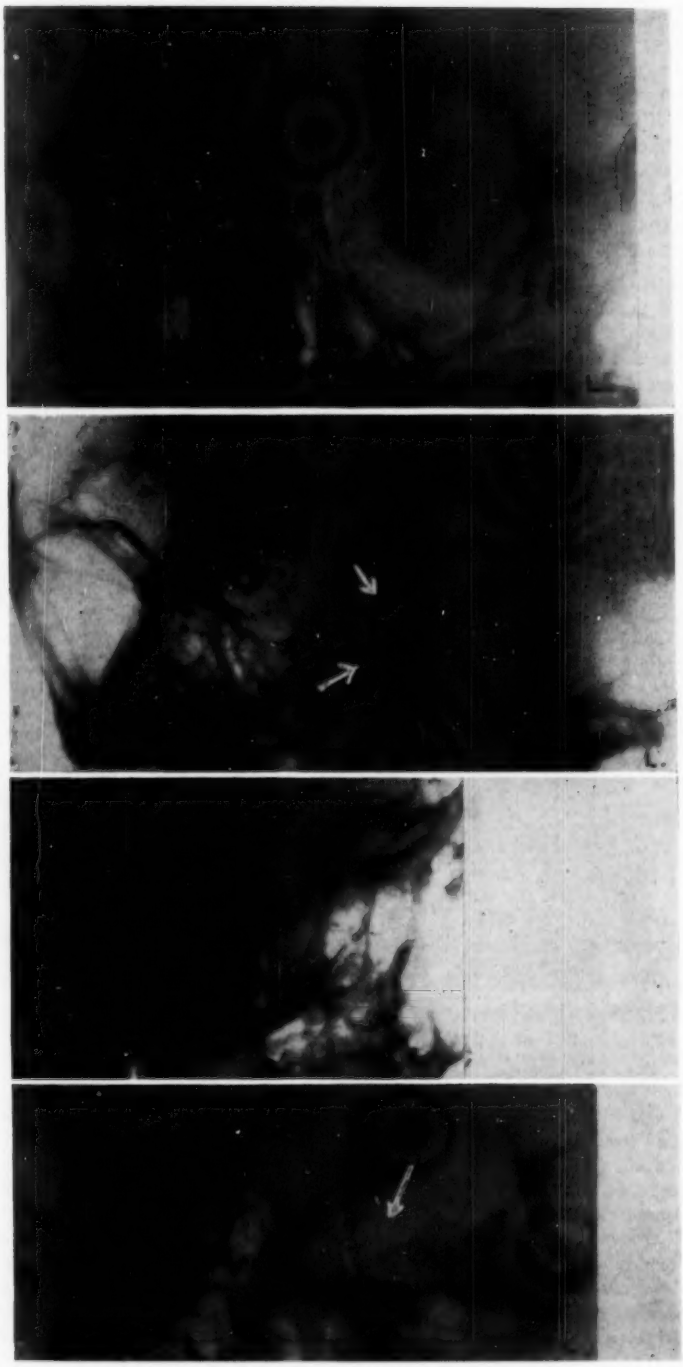

Fig. 3.—*A*, marked enlargement of the left orbit, with extensive destruction of the posterior and superior walls. A large rounded soft-tissue shadow can be seen within the orbit.

B, oblique view of the left orbit showing widening of the inferior orbital fissure, with extensive destruction of the greater wing of the sphenoid.

C, marked expansion of the sella turcica with sinking of the floor into the sphenoidal sinuses. Both the anterior and the posterior clinoid processes are intact.

D, posteroanterior view showing destruction of the apex of the left petrous bone.

The patient was readmitted to the hospital five months after operation for follow-up study. He was in excellent health, and his general appearance had improved tremendously (Fig. 2). One hardly noticed the operative scar. The lid was still slightly thickened and ptosed, but it could be raised a little with the help of the frontalis muscle. The eyeball showed the same degree of inward deviation as before the operation. The other findings remained unchanged.

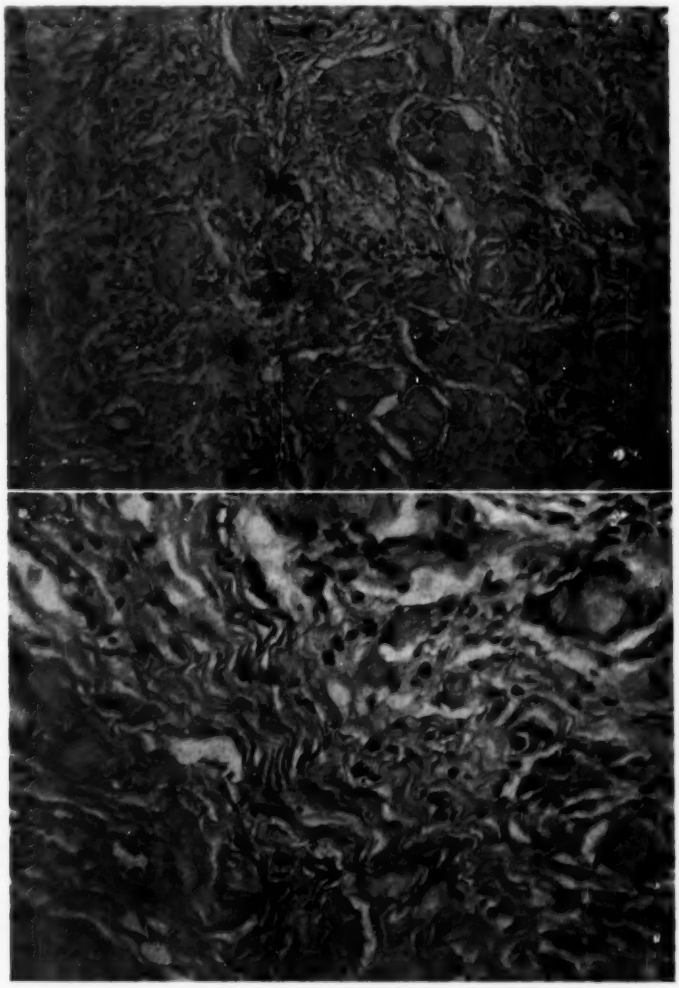

Fig. 4.—Photomicrographs of tumor removed from the orbit.

The neurological examination was again negative. It is interesting to note that the sensation to light touch was retained in the left upper lid. Repeat x-rays of the orbit and skull showed no change from those taken five months previously. The patient was discharged and was instructed to report back after six months.

COMMENT

The association of gliomas, gliosis, and meningiomas of the central nervous system with peripheral signs of von Recklinghausen's disease is well recognized. Such an association, however, with orbital involvement seems to be rare. I have been able to collect 25 cases from the literature, all of which presented strikingly identical features. To recapitulate, the characteristic findings are as follows: (1) an intracranial growth situated in the middle cranial fossa and extending to cause ballooning of the sella turcica; (2) a plexiform neurofibroma involving the orbit and very often the globe, the optic nerve, and the eyelids, with enlargement of the orbital cavity and defects in its walls; (3) café au lait pigmentation of the skin. Occasionally typical neurofibromata are also found.

As to the nature of the intracranial growth, the few cases with autopsy revealed a glioma, type astrocytoma (Davis *; Peyton and Simmons [1]). In the case presented a craniotomy was not attempted. It was felt that as long as the patient showed no signs of increased intracranial pressure a craniotomy was not indicated, since these tumors are slowly progressive and at best are very difficult to remove surgically. Ballooning of the sella turcica is very common, but pituitary dysfunction seems to be rare. The case presented revealed no signs of any dysfunction in spite of the extreme ballooning of the sella turcica. The optic chiasm did not seem to be involved to any degree, since perimetry showed no visual defects. Furthermore, there was no gross involvement of the optic nerve and globe.

The absence of pulsations in spite of the large defects in the walls of the orbit is of interest. Rockliffe and Parsons,[4] Foster Moore,[8] LeWald,[9] and Wheeler [10] called particular attention to this sign whenever a large defect was present. Its absence in this case cannot be explained.

SUMMARY

A case of plexiform neurofibroma of the eyelid and orbit with dilatation of the orbit, defects in its walls, and enlargement of the sella turcica and middle cranial fossa is presented.

A review of the literature reveals that 25 cases with almost identical features have previously been reported.

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Annual Reviews

PHYSIOLOGIC CHEMISTRY OF THE EYE

A Review of Papers Published During 1953

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THIS REPORT is comprised principally of material published during 1953 on the physiologic chemistry of the eye. In order to make it more comprehensive in scope, data on related subjects have been included.

CORNEA

The results of a study on the mucoproteins and mucopolysaccharides of the cornea, reported by Woodin and reviewed here last year, were in disagreement with early investigations of K. Meyer and co-workers; Woodin stated that the isolated fractions were resistant to testicular and bacterial hyaluronidases. In a study of considerable merit, Meyer and associates [1] reinvestigated the mucopolysaccharide fractions of the bovine cornea and isolated three components. The first fraction was identified as chondroitin sulfate; it was hydrolyzed by testicular, but not by pneumococcal, hyaluronidases. The separation of the second fraction presented great difficulties, which have not as yet been fully overcome; this fraction showed a low sulfate content and was hydrolyzed by testicular and pneumococcal hyaluronidases at a rate comparable to that of hyaluronic acid. This component, then, resembled hyaluronic acid. The third, and largest, component, which represented about one-half of the total mucopolysaccharide fractions of the cornea, was a sulfated mucopolysaccharide, for which the name keratosulfate is proposed. It seems to be the only sulfated polysaccharide of animal origin which does not contain uronic acid as one of its main constituents, and it is composed of equimolar quantities of glucosamine, acetyl, galactose, and sulfate. Gardell [2] describes a chromatographic technique for the isolation of glucosamine and galactosamine from a crude mucopolysaccharide fraction of the bovine cornea. After separation of the mixtures on Dowex 50 ion exchange resin (a sulfonated polystyrene exchange resin), quantitative recovery of the hexosamines was demonstrated. Using the original technique of Karl Meyer, Satoh [3] undertook a reexamination of the polysaccharides of fresh bovine corneae, with particular respect to their content of uronic acid. He confirmed Meyer's early results as to the presence of this substance. However, Meyer now considers this substance to be chondroitin sulfate. In addition, Satoh applied Dische's indole and orcinol reactions to the sample material and concluded from the results that glucuronic acid is the uronic acid component in the cornea polysaccharides. This conclusion is unfounded, since the techniques mentioned are not adaptable to such a determination.

Dr. Zacharias Dische, Biochemist of the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, aided in the evaluation of many of the papers reviewed.

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Several papers describing the application of histochemical techniques to the corneal mucoid and the storage glycogen in the corneal epithelium have been published. After a short historical introduction on the subject of corneal transparency, Aurell and Holmgren [4] report observations on metachromasia of the cornea, sclera, and tendon of rabbits, swine, and man. In untreated sections the well-known, sharply outlined staining contrast between cornea and sclera was evident. Treatment of such sections in running water for 48 hours dissolved the mucoid. When the sections of the cornea were placed in a mucoid solution, there followed an uptake of the metachromatic substance, whereas the sclera did not stain with toluidine blue under the same experimental conditions. In addition, collagenous and elastic fibrils of tendons did not absorb any mucoid, and connective tissue took up only very small amounts. The metachromatic substance found in the cornea of human fetuses was not equally distributed in early stages but was confined to the posterior layers of the cornea. The corneal stroma of 30 cm. human fetuses contained the metachromatic substance in all parts. In early phases the sclera also showed metachromasia, but at birth only traces of metachromatic material could be detected. François and Rabaey [5] studied the basophilia and metachromasia of the corneal mucoid and their dependence on the pH of the solutions of the dyes. At a pH range of 4.0 to 7.5, the corneal mucoid showed a rapidly increasing uptake of the dye, whereas sclera and Descemet's membrane remained unstained at a pH of 4.7. However, the specificity of the metachromatic stains gradually disappeared with increasing alkalinity of the dye solutions (above pH 5 all the tissues stain progressively). The authors feel that the high concentration of the corneal mucoid in the cornea hinders vascularization, and that only when the concentration is significantly reduced, as by edema, are the vessels able to grow into the cornea. This concept is similar to that of Karl Meyer, A. Braley, and others, who suggested that a decrease of the mucoids plays a part in the vascularization of the cornea. Günther [6] demonstrated a progressive decrease of metachromasia of the human cornea with time of storage. The stainability with toluidine blue remained unchanged for 12 days, then decreased, and disappeared at 30 days. Postmortal distintegration of the mast cells did not coincide with the loss of metachromasia, since the latter persisted for 18 days. The corneal elasticity and the metachromasia seemed to vanish at the same time. In a second paper,[7] the author lists observations which he made on disks of corneae from patients with various types of corneal scars. Toluidine blue and other stains were used on this material. The metachromatically staining cement substance appeared to be destroyed most extensively in eyes with lime burns and scars after gonoblennorrhea. Günther concluded that the preservation of metachromasia could be considered a prerequisite for successful keratoplasty. Histochemical examinations of the cornea of guinea pigs by Smelser and Ozanics [8] showed exhaustion of the storage glycogen in the corneal epithelium of animals which had worn specially fitted contact lenses. This depression of epithelial glycogen preceded the development of corneal swelling and corneal turbidity. The authors had shown previously that an adequate oxygen supply can prevent swelling of the cornea which results from contact lenses; they, therefore, express the belief that a metabolic process is involved in the water regulation of the cornea, with the energy required for this process very likely furnished by the glycogen store in the epithelium. Grethe and associates [9] examined histochemically the effect of monoiodoacetic acid, phlorhizin, and hyaluronidase on the activity of the alkaline

phosphatase of the bovine corneal epithelium. They used Gomori's technique for demonstration of the enzyme and sodium glycerophosphate as the substrate. The results indicated that contact of the preparation with monoiodoacetic acid and phlorhizin for 48 hours depressed the phosphatase activity. Pretreatment with hyaluronidase did not affect the depression by these two substances. This depression is most probably due to an inhibition of phosphorylation of glucose.

Among the studies dealing with the metabolism of the cornea, the following are worth noting: Heald and Langham [10] studied glycolysis in the living and the excised cornea of rabbits, using as an indicator the rate of accumulation of lactic acids under various experimental conditions. The results indicated that lactic acids accumulated in the living animals at a rate of 6.5 γ per milligram dry weight per hour. Under anaerobic and aerobic conditions, lactic acid accumulated at a rate of 10.5 and 2.76 γ per milligram dry weight per hour, respectively. From these ratios it is inferred that maximal respiration is not maintained in the living animal. The same authors [11] devised a beautiful method for determining the oxygen concentration in the aqueous humor of rabbits polarographically. The partial oxygen pressure of the normal rabbit eye was determined to be approximately 40 mm. Hg. When the animal, under artificial respiration, was placed in an atmosphere of oxygen, the partial oxygen pressure in the aqueous humor was found to rise until, after three to four hours, a steady-state value of about 90 mm. was reached. The amount of oxygen calculated to pass across the cornea was considered to be inadequate to maintain respiration of the tissue under normal conditions. From a preliminary study on the corneal respiration, Desvignes, Baron, and van Nham [12] concluded that the endothelium has the highest oxygen quotient (QO_2) and seems to play a predominant role in the respiration of the cornea. Since the results are in gross disagreement with those of previous investigators and details of the experiments are not given, a full report of the completed study will be necessary before evaluation. In the first of three studies on the dehydrogenases of the cornea, Jaeger [13] determined the activity of these enzymes in the total steer cornea, in the scraped-off corneal epithelium, and in the stroma, with and without endothelium, against various substrates, such as citrate, lactate, succinate, pyruvate, and glucose. These activities were tested by the triphenyltriazolium chloride (TTC) method. Dehydrogenase activity on glucose, succinate, lactate, and pyruvate was demonstrated in the corneal epithelium. The TTC reduction by the separated epithelium accounted for 60% of the activity of the total cornea (3% for endothelium, 1% for the stroma). Only glucose led to a significant increase in the reduction of TTC, due to a saturation of the enzymes by endogenous material. After the separated epithelium was washed, the endogenous reduction was eliminated and each of the above-mentioned compounds except pyruvate was found to lead to the reduction of TTC. However, the sum of the reduction by separated epithelium and stroma was lower by 40% than the original reduction by the total cornea. The author's assumption that this finding indicates an interrelating synergism between stroma and epithelium seems questionable, as the results could be explained by the damage to the epithelium; the conclusion, also, that the presence of dehydrogenases for succinate and citrate indicates the predominance of the tricarboxylic acid cycle does not appear well founded. In a second paper,[14] Jaeger deals with the role which inhibition of dehydrogenases may play in the production of corneal inflammation by toxic substances. Acids and alkalis destroy dehydrogenase activ-

ity as they destroy the tissue. In contrast to bacterial toxins, bee and snake venoms and copper salts interfere with the function of the dehydrogenases. This effect was observed to precede the development of the keratitis by several hours. Normal corneal epithelium acted as a partial protective barrier; thus, much higher dilutions of the poison were found effective on the excised cornea and in the coagulation test on egg yolk. Acrolein, allyl mustard oil, chloroacetophenone, and formaldehyde inhibited the dehydrogenases for lactic, citric, and succinic acid, and in concentrations which reduced dehydrogenase activity by more than 50% these substances produced keratitic changes. In the third part of this extensive investigation, Jaeger [15] examined the effects of commonly used therapeutic agents on the dehydrogenases of the cornea. As in the previous studies, he correlated in vivo and in vitro results obtained by the TTC reaction and the results of the coagulation test on egg yolk. In confirmation of the work of Hermann, Moses, and Friedenwald, he observed that the damaging effect of cocaine and tetracaine seemed to be caused by the inhibition of the dehydrogenases. Histamine interfered with the TTC reaction only in very high concentrations, and sulfonamides did not exert a marked inhibition. A great number of experimental data on the relation of anti-inflammatory agents to irritating and toxic substances of varying nature were presented. Complex-forming agents, such as sodium thiosulfate, antihistaminics, and, in great detail, zinc salts, were studied. The most striking results were obtained in the blocking of inflammatory responses to bee and snake venom by zinc sulfate and zinc acetate. It did not seem likely that the zinc salts reacted directly with the poison; rather, it was probable that they competed with the poison in the inhibition of the dehydrogenases. Jaeger's interesting observations led to important practical conclusions, which are discussed in the last part of the paper. The TTC reaction also was used by Köhler, Fürst and Scharf [16] on disks of calf corneae in a study of the effect of desoxycorticosterone acetate (DOCA) on the dehydrogenase activity at different temperatures. The augmentation of this activity by the hormones was of low magnitude in fresh corneae at low temperatures, but was considerable in 24-hour-old preparations at all temperatures tested. Under these conditions, the time-induced loss of activity was regained almost completely under the influence of desoxycorticosterone acetate solution in a concentration as low as 1 : 1,000,000.

Various aspects of the problem of corneal permeability are reviewed in the thesis by Maurice.[17] The subject is divided into an historical introduction and a discussion of the permeability of ionic and nonionic substances. Special reference is made to the author's own previously reported work on permeability to Na^{24}. Other small series of experiments by Maurice have dealt with the relative binding power of excised cornea for methylene blue and fluorescein solutions, and the controversial issue of the directional permeability of the cornea to gases. The many contradictory observations of various research workers, and the consequent difficulty of arriving at a tenable theory, were brought out in the critical analyses of the author. The comparison of results and the assessing of interpretations might have been facilitated if the author had had direct contact with such investigators still active in this or related fields, although the obstacles of dealing with reports in which far-reaching conclusions are based on a small number of experiments and control experiments are of questionable nature could hardly be overcome. In view of the nature of the paper, with its extensive critical analysis, it is possible to men-

tion here only some of Maurice's conclusions and to refer the interested reader to the study of the original article. Despite results of conflicting nature, Maurice assumed that the permeabilities of the limiting membrane of the cornea to ions of small molecular size are in the same range of magnitude. This would suggest that these ions pass through extracellular spaces. On the assumption that the space between the cells is filled with a fluid no more viscous than aqueous humor, the diameter of the largest particle which can pass across the cellular layer is estimated to be in the range of 10 to 25 A. Of general importance is the author's impression that increases in the permeability of the cellular layers can easily be effected by touching the eye or by instilling or injecting solutions in the eye, especially when these solutions deviate greatly from the tonicity of the body fluids. The question of a directional, or irreciprocal, permeability of the cornea cannot be answered at the present time on the basis of available data. The same situation applies to the question of the flow of aqueous humor through the limiting corneal layers. In addition to exchange by passive diffusion of substances dissolved in the cornea with those in the plasma and in the aqueous humor, there may be at work a mechanism of active transfer of some substances out of the cornea. Such a transfer may help the maintenance of the normal corneal thickness.

Potts [18] designed several promising experimental procedures for investigating various phases of the problem of the permeability of corneal epithelium and endothelium to inorganic salts. In the experiments carried out on living animals under pentobarbital anesthesia, the permeability of the anterior corneal surface in an outside-in direction, the diffusion from a depot placed in the corneal stroma, and the diffusion from the aqueous humor into the cornea were examined. The first group of experiments was done with sodium chloride labeled with Na^{22}, sodium phosphate labeled with P^{32}, and cesium chloride labeled with Cs^{134}. The minimum penetration into the epithelium coincided with a concentration of labeled salts equivalent to 1.35% sodium chloride. This, by inference, appears to be the tonicity of precorneal tear film. Radiosodium, radioiodide, and radiophosphorus served for the determination of diffusion from a depot in the cornea and from the aqueous humor into the cornea. The results indicated a low permeability of the corneal epithelium to inorganic salts in both directions, whereas the corneal endothelium apparently exhibited good permeability in either direction, especially from an intracorneal depot to the aqueous. Before the results of the latter group of experiments can be accepted, it will be necessary to prove that the unavoidable trauma to pertinent structures did not influence the results significantly. The permeability of the rabbit cornea to cations and anions was studied by Kikkawa,[19] who placed the tissue between two salt solutions of different concentration and applied a potential difference. The excised cornea reduced the mobility of the anions considerably more than that of the cations. The retardation of the anions might be due to the negative charge of the tissue. Calcium ions seemed to be either adsorbed or precipitated on the surface of the cornea; they still diffused easily from outside in, and less readily in the opposite direction. The importance of the barrier qualities of the posterior surface of the cornea is suggested by Bock and Maumenee,[20] who attempted to introduce a thin sheet of water-impermeable polyethylene film beneath the epithelium and another sheet anterior to the endothelium of the rabbit's cornea. However, the unavoidable severe trauma of such a procedure makes any conclusion based on these observations difficult to evaluate.

Orzalesi and Ciuffo [21] report on histologic and physicochemical changes of corneal transplants during preservation. In rabbits, intracutaneous injection of extracts of steer corneae preserved at various temperatures were used for the trypan blue test of Menkin. The positive results varied with the length of preservation of the corneal tissue, from 100% negative results in fresh corneae to 100% positive results in corneae preserved for eight days or more. The results were more strongly positive in the excised corneae than in the corneae preserved in the intact eye. Raising the temperature of preservation increased the rate of development of positive results. It was concluded that during preservation of corneal tissue autolysis of corneal proteins produces substances which can cause inflammatory reaction—especially increased capillary permeability—and that these substances are not identical with histamine but act in a similar way. Probably the changes in the transplant are due to a reaction of an allergic nature between the transplant and the host, an opinion which was expressed by Maumenee several years ago.

Sakaki [22] measured the pH of the rabbit cornea in vivo by the quinhydrone electrode method. The technical difficulties which had to be overcome must have been very great. The pH values given in this paper are 7.42 for the corneal epithelium and 7.58 for the stroma.

Desvignes [23] contributes a brief review of the chemistry of the cornea.

In their report of the study by phase-contrast microscopy, François and Rabaey [24] describe a technique by which they claim to render visible collagen and mucoid selectively and separately. When the preparations were mounted in Canada balsam or in Clarite, an irregular network was noted which may correspond to the mucoid; after formol fixation and embedding in paraffin, preparations suspended in water showed the collagen lamellae. In Yamamoto's [25] phase microscopy study of the rabbit cornea, a membrane similar to Bowman's membrane was recognizable, in contrast to the apparent absence of such a membrane with the usual histological techniques. Outstanding in experimental approach and documentation of results are two electron microscopic studies by Schwarz on the structure of the human sclera and cornea. The preparations were treated with osmium tetroxide and with the silver impregnation technique of Gomori. In the first paper,[26] the similarity of the scleral fibers to the collagen of tendon fibers is stressed, whereas the fine corneal fibrils could be compared to embryonic fibers of connective tissue. The average thickness was 29 mμ. The fibrils of the cornea were shown to be embedded in a coat of cement substance, a part of which belonged to the substrates of hyaluronidase. Sclera or tendon contained much less of this substance. The corneal fibrils, which were arranged in bundles 2.5 to 8 μ in thickness, were masked by the cement substance. These submicroscopic fibrils, with a masking of cement substance of similar refractive index, are thought by the author to be responsible for the transparency of the cornea, in contrast to the opaqueness of the sclera. Any change of the fibrils or the cement substance, or a shift in their physical and chemical interrelation, could lead to a loss of corneal transparency. In a second study, Schwarz [27] reports his observations on various stages of development of corneal and scleral tissues. Material from fetuses of 2.5, 4.0, 8.5, and 16.5 cm., up to the adult, was studied. The appearance of the corneal fibrils did not change throughout the various stages of development, whereas the scleral fibrils underwent a process of differentiation during these

periods which resulted in the formation of the mature, thick collagen fiber. Cornea and sclera both remained transparent in fetal life up to the length of 8.5 cm. It was from this age that the scleral fibers gained in thickness, with a simultaneous decrease in the cement substance and a progressive loss of transparency. In contrast to these changes in the scleral fibers, the corneal fibers remained in an early stage of differentiation. Samples from scarred corneae showed a differentiation of the fine corneal fibrils to mature collagen.

Using a polarizing microscope, Kikkawa [28] studied the rabbit cornea and reported that, optically, corneal fibers are a biaxial and negative crystal. The Y- and the Z-axis lie in the tangential plane of the cornea; the former lies in the direction of the long axis of the fibers, and the latter, perpendicular to it. The X-axis is in the direction perpendicular to the tangential plane. This relationship can be clearly observed in the periphery of the cornea, where the fibers are arranged regularly in a radiating direction. At the center of the cornea, where the arrangement of the corneal fibers is extremely irregular, the cornea appears to be "uniaxial and negative." When the fiber is stretched in the direction of its arrangement, the Z-axis rotates by 90 degrees.

AQUEOUS HUMOR

By means of an ingeniously designed and well-controlled technique, Kinsey [29] succeeded in studying the concentrations of osmotically active constituents of pure samples of aqueous humor from the posterior chamber, and in comparing them with the concentrations of these substances in the fluid of the anterior chamber and in the plasma. In a previous study Kinsey demonstrated that the osmotic pressures of the aqueous humor in the two chambers are about the same, but that the ascorbic acid content of samples from the posterior chamber exceeded by about one and one-half times the concentration in samples from the anterior chamber. In the present work these results were confirmed; in addition, Kinsey found a relatively higher content of bicarbonate in the aqueous humor of the posterior chamber and showed that the concentrations of chloride and phosphates in the posterior chamber were less than in the anterior chamber. The pH values of the two intraocular fluids, as determined by a colorimetric method, did not differ significantly (7.57 and 7.6) but were higher than the pH averages of the plasma (7.4). The observed pattern of distribution of these concentrations in plasma and aqueous humor in the anterior and posterior chambers provided supporting evidence for Kinsey's concept that chlorides and phosphates enter the posterior chamber by diffusion. They exist here in concentrations lower than in the plasma because of dilution by water, which enters the posterior chamber as a result of the hypertonicity created by bicarbonate, ascorbate, and certain cations. The concentration of bicarbonate in the posterior chamber, which is higher than that in the plasma and in the anterior chamber, points to an active secretion of this constituent by the ciliary body. In Kinsey's opinion, the permeability of iris vessels is limited to anions and nonelectrolytes, although in the present study no data were given regarding the permeability to sodium and potassium. On the basis of the distribution of chloride, phosphate, and bicarbonate, Kinsey concludes that a process of simple diffusion governs the transfer in the anterior chamber. In direct contrast to this conclusion of Kinsey is the interpretation of Heer [30] that chlorides enter the aqueous humor

by secretion. Since Heer's experiments were limited to a small number of animals and to seven patients with hydrophthalmos, the evidence is not sufficient to substantiate his rejection of diffusion as the mechanism.

The role of ascorbic acid in the transfer of aqueous humor across the blood-aqueous barrier was studied by Scholz [31] on normal and scorbutic guinea pigs. Using Na^{22} as tracer, he determined the steady-state ratio of sodium of the plasma water to sodium of the aqueous humor. This rate was determined as $\pm$ 0.985 in the normal animals, as against $\pm$ 1.055 in scorbutic animals. Thus, in the absence of ascorbic acid the secretion of sodium into the aqueous was diminished and the ratio approximated that of a dialysate as calculated for the Donnan equilibrium. The results provide confirmation of Friedenwald's concept of the importance of ascorbic acid in the formation of intraocular fluid. Davson and Matchett [32] undertook an extensive study of the kinetics governing the process of penetration across the blood-aqueous barrier of three sulfonamides, thiourea, and sucrose. Moreover, the results of less complete experiments with thiocyanate, Na^{24}, *n*-propyl thiourea, and raffinose are included in this outstanding piece of work. It was shown that for several substances the relationship between k_{in}, that is, the inward transfer constant of a penetrating substance, and r, the steady-state distribution ratio between aqueous humor and blood plasma, does not conform to the equation derived by previous workers. The reformulation of the mathematical treatment of aqueous humor kinetics, important as it is, is beyond the scope of this review and should be studied in the original. The results of these measurements and those concerning the effects of nitrogen mustard and unilateral occlusion of the carotid artery were the basis for the revival of the concept that a dual process is involved in the penetration of a given substance across the barrier: secretion of solutes by the secretory cells of the ciliary epithelium into the posterior chamber, and diffusion by an intracellular route through the iris capillaries into the anterior chamber.

A series of experiments was carried out by Davson [33] to determine whether large water-soluble molecules entered the aqueous humor by bulk flow of fluid through the relatively large water-filled intercellular spaces or by simple diffusion. The entry of raffinose was compared with that of *p*-aminohippurate. The mean percentage of the rates of these two substances with a molecular weight differing by a factor of 2.6 was only 6% in favor of *p*-aminohippurate. It was concluded, therefore, that such substances are carried into the aqueous humor predominantly by bulk flow. The value of Davson's review article [34] on "problems concerning the formation and circulation of the aqueous humor," as a comprehensive summary, is enhanced by the author's discussion of his own work and the evaluation of the current work by other investigators in this field. The report deals mainly with kinetics of the blood-aqueous barrier. Davson feels that it is too great a simplification to assign a single parameter to the transfer of a specific substance from the plasma to the aqueous humor. Instead, he suggests that three processes might compete with each other: secretions by the ciliary epithelium, diffusion from the posterior surface of the iris, and, most important, diffusion from the anterior surface of the iris. The average concentration of the substances in the aqueous humor results from a mixture of the contents of the "primary" aqueous humor in the posterior chamber, and the accumulation of substances which entered the

anterior chamber by diffusion. Tsutsui and Nagata * used a polarographic method to measure the transference of metal ions from blood to aqueous humor in rabbits.[35] Quantitation of the permeability of the blood-aqueous barrier based on the ion content of the aqueous humor was considered of questionable validity, since metal ions, such as $Co^{\cdot}$, $Zn^{\cdot\cdot}$, $Ni^{\cdot\cdot}$, and $Mn^{\cdot\cdot}$, have an affinity for albumin and effect contraction of the blood vessels. The ion content of the aqueous humor was generally low and in the order of $Zn^{\cdot\cdot}$, $Co^{\cdot}$, $Ni^{\cdot\cdot}$, and $Mn^{\cdot\cdot}$. The amount of manganese and nickel present was about equal to that in venous blood. When marked changes occurred in the metal ion content of the aqueous, the chlorine content also changed, but to a less pronounced degree. In the absence of metal ions, the Cl^{-} content of the aqueous humor was lower than that of the arterial blood, which, in turn, was lower than that of the venous blood.

The advantages of paper electrophoresis, which was first used by Witmer for the study of proteins of the aqueous humor, continue to attract ophthalmological research workers. Münich [36] reports several experimental series in which this method was utilized in study of the primary and secondary aqueous humors and of the serum of rabbits. In the secondary aqueous, a relative increase of the albumin fraction and a decrease of the globulin fraction were noted by comparing the readings with those obtained on the serum. A rise of body temperature induced by injection of a foreign protein preparation produced a well-marked albumin peak in the aspirated samples of aqueous humor, in contrast to the minimal quantities which could be demonstrated in untreated (control) animals. Chinaglia and Franca [37] used paper electrophoresis in determination of the proteins of the aqueous humor and the blood serum of a very inhomogeneous group of 24 patients with inflammatory changes of the eye. With respect to its accuracy, the method used for the protein determination is open to criticism and scarcely provides more than rough estimates. This reviewer agrees with the authors that no definite conclusions can be drawn from their results, which suggest an increase of the alpha-globulin fraction in the aqueous humor as compared with this fraction in the blood serum of the same subject. Obviously, much more experimental material is necessary to permit quantitation of electrophoretic data on the subfractions of the globulin in the aqueous humor. Two-dimensional paper chromatography, with phenol and lutidine as solvents, was used by Blaha and associates [38] to separate the amino acids in the aqueous humor and the serum of rabbits. The authors felt that they could identify glycine (aminoacetic acid), serine, alpha-alanine, glutamic acid, leucine, gamma-butyric acid, threonine, hydroxyproline, and phenylalanine. From the same quantities of aqueous humor and serum, amino acid spots were produced which were similar in size and intensity of color. This was interpreted as indicating that amino acids in the aqueous humor and in the serum exist in identical concentrations. Here the question should be raised as to the reliability of differences in color intensities as a method of quantitation of paper chromatograms. The conclusion of the authors that the amino acid entered the anterior chamber by diffusion, and not by secretion, is not in full agreement with the findings of Duke-Elder, who described an extremely slow penetration of alanine and glycine across

* Despite the cooperation of Dr. Yukihiko Mitsui, of Kumamoto University Medical School, I was, in general, unable to obtain translations of the Japanese papers and had to rely on published abstracts. It is impossible, therefore, to assess properly the significance of the results and the value of the observations.

the blood-aqueous barrier. Malatesta [39] also used paper chromatography in his study of the distribution of amino acids in ocular fluids and tissue, but the results are tabulated in a way that makes it impossible to abstract the paper. All amino acids of the blood, with the exception of phosphocolamine, beta-alanine, proline, and tyrosine, pass into the aqueous humor. The last-mentioned three amino acids were not visible in the fluid phase of the vitreous or the lens.

Böck and Hellauer [40] tested pharmacologically the histamine activity of human aqueous humor from normal and glaucomatous eyes and that of the aqueous humor of the guinea pig, rabbit, and steer. The isolated intestine of the guinea pig in oxygenated Tyrode solution was used in bioassay of the samples. In most instances, normal aqueous humor, even when pooled, did not contain enough histamine to elicit threshold responses of the preparation. The results of the majority of previous examiners on normal eyes were thus confirmed. Moreover, Böck and Hellauer concluded from their experiments that the aqueous humor of eyes with primary glaucoma was either free of histamine or contained only insignificantly small amounts of this substance. A slight increase in the tone of the guinea pig preparation, occasionally produced by samples of aqueous humor of normal and glaucomatous eyes, appeared to be caused by a substance which was definitely not histamine but possibly related to the vasoactive substance demonstrated previously in nerve elements by Hellauer and Umrath.

Sugawara's [41] report on the cholinesterase content in aqueous humor confirms the findings of previous investigators in that only traces of this enzyme were found in the aqueous humor and the activity rose after paracentesis. The increase disappeared within 24 hours. In the primary aqueous of atrophic eyes no enzyme could be detected. Tolazoline (benzylimidazoline) depressed the enzyme activity slightly, whereas vagostigmine (a Japanese neostigmine preparation) and diisopropyl fluorophosphate were more effective inhibitors.

In a series of three studies, Nagata compared changes in the aqueous humor and the cerebrospinal fluid of normal rabbits under various conditions. The protein contents of the normal aqueous humor and cerebrospinal fluid did not differ significantly, and changes of diet did not exert any noticeable influence.[42] In marked contrast to the unchanged protein content of the cerebrospinal fluid formed after cisternal puncture, the secondary aqueous had a high protein content. The well-known influence of subconjunctivally administered epinephrine on the reduction of the protein content in the primary aqueous was not noticed on the secondary aqueous humor after paracentesis.[43] An increase of the protein content of the primary, but not of the secondary, aqueous humor was observed after subconjunctival injection of pilocarpine. Intravenous injection of epinephrine (0.2 mg.) was followed by an increase in the protein content of the primary aqueous and the first cerebrospinal fluid, while no effect on the protein concentration of the second fluid was evident. Epinephrine injected intraspinally caused a decrease in the protein level of the secondary cerebrospinal fluid. Finally, Nagata extended the study [44] to the transmission of foreign protein injected intravenously into the aqueous humor and the cerebrospinal fluid; the oxygen consumption of the tissues which produced these fluids was studied. Ten per cent egg albumin increased the protein content of the first cerebrospinal fluid, but not that of the first and second aqueous humors and the second cerebrospinal fluid. When the concentration was increased to 15%, the protein concentration rose in the first and second aqueous humors and

in the first cerebrospinal fluid. Iris and ciliary body consumed 30 to 40% less oxygen after paracentesis. Instillation of epinephrine and pilocarpine did not change the QO_2 of iris and ciliary body. The oxygen consumption by unit weight of arachnoid appeared higher than that of iris and ciliary body.

Spitzy and Skrube [45] described a sensitive micromethod for determining minimal amounts of iodine in the aqueous humor of rabbits. It is a modification of Winkler's titration procedure and is based on the oxidation of iodide by bromine to iodine and titration of the latter with thiosulfate. Amounts of 0.1 γ per 0.1 gm. of aqueous can be determined by this technique. The method of Spitzy and Skrube was used by Hagmüller, Hellauer, and Spitzy [46] in a study in which eyes of rabbits either were exposed to a spray of iodide mineral water (content 17.7 mg. of iodine per 100 cc.) for 20 minutes or were treated with two drops of the same water. These procedures resulted in a steep rise of the iodine content in the aqueous, with a maximal value of 0.23 mg. per 100 cc. at the 30-minute interval; the zero level was reached after 16 hours. As expected, the penetration of the halogen was accelerated when applied in hypotonic solution. Frequent instillations of hyaluronidase prior to the use of the iodide mineral water did not increase the permeability of the cornea for the test substance. The steep fall of the appearance rate curve in the period between 30 and 120 minutes was thought by the authors to be caused mainly by diffusion, but also by convection. It should be added, however, that the binding of iodine to organic matter may contribute to the disappearance rate from the aqueous humor. Such a factor was strongly suggested in older experiments, in which the distribution of radioactive iodine was studied by radioautography. Obviously, the iris takes up considerable quantities of iodine introduced into the aqueous humor.

Matsuura conducted a series of studies on the influence of the ciliary arteries on the production of the aqueous humor. It will suffice to mention here that the fluorescein appearance curve for the aqueous humor reached its peak 30 to 50 minutes after intravenous injection and then fell gradually, and that a certain parallelism existed between the rate of entry of the dye and the changes in the intraocular pressure.[47] The protein content was found to be increased [48] when the intraocular pressure had risen, and the level remained high even after restoration of the normal pressure.

From the results of experiments in which Sapuppo [49] used the rate of entry of fluorescein across the blood-aqueous barrier as an indicator, the author concluded that beta-pyridil carbinol is more effective than nicotinic acid in increasing the permeability of the blood-aqueous barrier.

Vitamin E was administered by Marisco [50] to a small number of rabbits with diabetes produced by alloxan. It was observed that the vitamin lowered the glucose level both in the blood serum and in the aqueous humor. In view of the small number of observations, the statistical validity appears questionable.

Gemolotto [51] determined the content of ascorbic acid and glucose in the aqueous humor of rabbits prior to and after the intravenous injection of sodium iodate. At the time when the retinal damage had fully developed, the glucose concentration showed higher values, and the ascorbic acid definitely lower values, than the premedication levels. The concentration of these substances in the blood remained the same. The possibility of reduction of ascorbic acid to glucose considered by the author appears highly improbable.

LENS

The results of an investigation conducted by Dische and co-workers [52] on glutathione and nucleotides of the lens capsule require revision of the presently held concept of the inert nature of this membrane. It was shown that the relatively high content of glutathione and nucleotides in the lens capsule cannot derive from postmortal diffusion of these substances from the superficial cortical fibers or from the lens epithelium into the capsule. The amount of glutathione corresponds to 15 to 30% of that in the surface layers of the lens cortex; the amount of nucleotides, to 30 to 40% calculated per 100 mg. wet weight. In the presence of air and at room temperature, rapid oxidation of glutathione takes place; anaerobically, ribose of the nucleotides is broken down to unidentified end-products. Fujimoto,[53] in his study on distribution of reduced and oxidized glutathione in the lenses of rabbits and steers, arrived at averages of 251.228 and 19.165 mg. per 100 gm., respectively, for the rabbit lens, and 212.117 and 4.9143 mg. per 100 gm. for the steer lens. At first glance these figures appear low as compared with previously reported values, but they cannot be evaluated without detailed knowledge of the technique. Both types of glutathione were present in largest quantities in the cortex, especially in the equatorial portion.

In a continuation of their previously reported study on the significance of changes in the potassium and sodium content of the lens, Harris and co-workers [54] carried out an important investigation of the lenticular cation shift under the influence of low temperature and calcium deficiency. Loss of potassium and gain of sodium observed in the refrigerated lens preparation was reversed when the temperature was raised; addition of calcium to a calcium-deficient medium restored the normally high potassium and low sodium content of the lens. Harris' original concept of a balance between an active transfer mechanism which governs the distribution pattern of the two cations in the lens and a process of passive diffusion of the cations in the opposite direction along a concentration gradient was substantiated by these results. Studies were also undertaken by Desvignes, Baron, and Delaunay [55] on the movements of sodium and potassium in the normal and cataractous lens; in contrast to the findings of Harris and co-workers, no decrease in the potassium content was observed in cataractous lenses, whereas such lenses gained markedly in sodium. A change in the permeability of the cataractous lens for sodium is assumed by the authors. Such results, showing an increase in sodium without corresponding decrease in potassium, are incomprehensible.

Mandel, Nordmann, and Bloch [56] determined the amount of chloride, sulfate, phosphate, carbon dioxide, organic acid, sodium, potassium, calcium, and magnesium present in the fish lens. They used Volhard's method (Cl^-), Van Slyke's method (CO_2), Marenzi and Banfi's method (SO_4^{--}), and ultrafiltration (cations). Sixty-seven per cent of K^+ and 69% of Na^+ were found ultrafiltrable. Calcium of the calf lens, but not of the steer lens, could be demonstrated after ultrafiltration. As expected, Cl^- was completely recovered in the ultrafiltrate. The predominance of the cellular potassium over the extracellular sodium could not be explained by considering the epithelium alone, but it points to the cellular nature of the main mass of the lens. The soluble proteins of human lenses, as well as those of ox, horse, pig, monkey, and rabbit lenses, were subjected to paper electrophoresis by François and co-workers.[57] In the human and monkey material four fractions could be differen-

tiated, whereas in the other species studied three fractions were found. The values for the individual fractions varied with each species and with the portion of the lens examined. Interestingly, the electrophoretic pattern from the normal human lens did not differ from the cataractous lens of patients of the same age. Malatesta [58] analyzed the free amino acids in the lens by means of paper chromatography. From the reproduction of the chromatogram, it can be seen that phosphoserine, glutamic acid, glycine, alanine, serine, and taurine are present in greater quantities than are leucine, valine, and phosphocolamine.

Various aspects of the synthesis of ascorbic acid by the rabbit's lens were studied by Yamamoto, Ogino, and Higuchi.[59] The capacity for synthesizing ascorbic acid from 2-keto-gulonic acid disappeared in the homogenate of lenses which had been made cataractous by needling three days prior to the removal of the eyes. The addition of heat-inactivated extracts of normal lenses or muscle tissue restored this capacity. Reactivation was not possible, however, when seven days had elapsed (Yamamoto). The ascorbic-acid-synthesizing action of young animal lenses exceeded that of the lenses of aged rabbits (Ogino). Higuchi [60] investigated the possible participation of Kreb's tricarboxylic acid cycle in ascorbic acid synthesis of the lens. Synthesizing action impeded by malonic acid was recovered by treatment with fumaric acid, but not by succinic acid. Neither fumaric acid nor succinic acid per se influenced ascorbic acid synthesis of the lens. The conclusion of the author, in which he states, according to the wording of the abstract, that ascorbic acid synthesis of the lens and the tricarboxylic acid cycle have no relationship, does not seem to be consistent with the reported results on the effects of fumaric acid on the synthesizing action impeded by malonic acid. This observation suggests at least an indirect influence of Kreb's tricarboxylic acid cycle on ascorbic acid synthesis. According to the report of Higuchi,[60] beef lenses contain an enzyme which apparently catalyzes the synthesis of vitamin C from 2-keto-*d*-gulonic acid. Inactivation of this enzyme by heating was reversed by addition of an enzyme inactivated by dialysis. In the author's opinion, the enzyme consisted then of two fractions, one dialyzable and thermostable, and the other nondialyzable and thermolabile. The addition of KCN accelerated the synthesis; $AgNO_3$ impeded it. Mishima [61] observed that malonic acid impeded the synthesis of ascorbic acid from mannose, but that the effect could be reversed by fumaric acid or by adenosinetriphosphate (ATP). If this observation is correct, it would indicate that ATP is necessary for synthesis of ascorbic acid from mannose. Ogino [62] demonstrated that the needled rabbit lens loses the capacity for producing dihydroascorbic acid from 2,3-diketogulonic acid by closing the lactone ring, and for dehydrogenating mannose to mannonic acid. In another study by Ogino and co-workers,[63] on the decomposition of ascorbic acid in cataractous lenses, oxalic acid appeared six days after needling. The authors concluded that the oxalic acid was the result of decomposition of 2-keto-gulonic acid. According to Uyama and co-workers,[64] an intraperitoneal administration of dopa quinone (30 mg. daily) in guinea pigs caused development of a gray cataract within three to four days. If 0.05 mg. of ascorbic acid was added to this treatment every day, the cataract developed after five days, and if this dose of ascorbic acid was increased to 0.2 mg. the development of the cataract was delayed an additional two days and the cataract was of a brown color. The dose of 2 mg. of ascorbic acid prevented cataract formation completely. The mechanism of this protective action of ascorbic acid is not discussed in the abstract. Yamada [65] demonstrated that treatment of vitamin C-deficient guinea pigs for 12 days

with intraperitoneal injection of sodium butyrate plus, on the last five days, oral administration of tyrosine resulted in development of cataracts. The urine of these animals contained considerable quantities of benzoquinone acetic acid. Elimination of sodium butyrate from the treatment prevented the development of cataract, and there was no marked excretion of benzoquinone acetic acid.

Reich and Healy [66] determined the content of carbonic anhydrase in homogenates of bovine lenses by the modified colorimetric method of Trethewie and Day. Slaughter-house material was obtained from animals in age groups of 5 months to 1 year, 2 to 9 years, and 10 years and over. All the lenses were free of cataractous changes. The carbonic anhydrase activity of normal bovine blood served as a standard for comparison. The average values of the lens enzyme activity in the three age groups did not show significant differences. Thus, the decreased enzyme action, previously described by Bakker in senile cataract, appeared to be caused by the cataractous process, and not by old age or by a precataractous state. Mandel, Zimmer, and Nordmann [67] were able to determine in calf lenses two types of pyrophosphatases—one with an optimal activity at pH 5.5, and the other, at a pH of 7. The same authors [68] demonstrated in bovine lens homogenates the presence of an alkaline phosphomonoesterase which appeared to act preferentially on beta-glycerophosphate at a pH of 7.4 to 8.2. In contrast to the findings of the preceding abstract, no acid phosphatases were detected. Fujimoto [69] studied glutathione reductase in rabbit lenses. When a buffered extract of rabbit lens was brought into contact with oxidized glutathione, glutathione was reduced. The enzyme was found to be heat-labile and partially impeded by the presence of silver nitrate. It lost its activity during dialysis, but such inactivated enzyme regained its activity when a heat-inactivated enzyme or diphosphopyridine nucleotide was added. Flavinadenine dinucleotide stimulated anaerobic reaction of the reductase. The conclusions of the author that reductase is one of the pyridine enzymes having diphosphopyridine nucleotide as coenzyme are difficult to reconcile with the results previously reported by Pirie and co-workers, who showed that triphosphopyridine is the coenzyme of glutathione reductase in the lens.

Ascorbic acid-reduced glutathione, protein SH groups, and various enzymes were determined by Pirie and co-workers [70] in extracts of rabbit lenses after the eyes had been exposed to 1,400 r of 200 kv. x-rays. Surprisingly, the first signs of lens damage were observed by slit-lamp examination as late as four months after irradiation. Estimation of the reduced glutathione indicated a decrease, with loss of 13%, at the three-month interval. This loss progressed to 85% at nine months after irradiation, when the cataracts were complete. The protein SH content did not drop significantly until about six months after exposure to the x-ray beam. A fall in glutathione reductase occurred at a four- to five-month interval after irradiation. A slight decrease of ascorbic acid in the aqueous humor after x-ray treatment did not seem to be correlated with the development of lenticular opacities. Therefore, the first change in the chemistry of the lens slightly preceded the development of gross cataractous changes at the time when histological examination should have shown extensive signs of radiation damage. As a contribution to the problem of chemical mediation of radiobiological effects, Zeller [71] determined the catalase activity of cattle, rabbit, and dog lens homogenates manometrically by following the liberation of oxygen. In these well-controlled experiments, the values, expressed in micromoles of oxygen per hour and per gram wet tissue, varied for rabbit and

cattle lenses from 30 to 100, and for dog lenses from 16 to 30. These values were lower than those reported in other tissues. The agent responsible for the decomposition of hydrogen peroxide was heat-labile, did not dialyze through membranes, and was blocked by typical catalase inhibitors. The minimal quantities in the samples would indicate that a sufficient protective effect by catalase against hydrogen peroxide, possibly produced during the irradiation, is unlikely.

Permutt and Johnson [72] attempted to characterize polysaccharide protein complexes in frozen-dried material of normal rabbit lenses and those in which cataracts had been produced by x-rays. They employed the method of Hotchkiss, and also a modification of this procedure, which apparently reduced the loss of stainable material occurring during the original technique. In addition, deparaffinized sections were stained for metachromasia with toluidine blue, and ultraviolet absorption of the lens fibers served as a means of determining changes in the protein concentration, according to the technique of Catchpole and Gersh. With the modified technique, the lens capsule, the cement substance between the fibers, and the lens fibers stained uniformly from red to pink. The cytoplasm of the epithelial cells contained reddish granules. When the original method was applied, only the lens capsule and the intrafibrillar cement showed the color reaction. This stained material was considered by the authors as a polysaccharide-protein complex. On the basis of solubility of this substance in distilled water, phosphate buffer, and hydrochloric acid, the authors distinguished two complexes. Epithelial cells and lens fibers contained material soluble in water and hydrochloric acid. On the other hand, the staining material in the capsule and the cement substance did not appear to be soluble in these solvents. The same techniques were also applied to cataractous lenses which were obtained six months after exposure to penetrating x-rays and slow neutrons in relatively high doses. Swelling of the lens capsule, the lens fibers, and the cement substance was accompanied by an increased color reaction with the Hotchkiss stain in these areas. The stainable material exhibited an increased solubility in water and acid as compared with normal lenses. This change was thought to be due to depolymerization of the ground substance of the lens under direct influence of the radiations on the polysaccharide-protein complex, in a manner similar to the breakdown of proteins by irradiation.

In connection with previous studies on the phosphate metabolism of the lens, Müller and Kleifeld [73] examined the uptake of P^{32} from the nutritive environment by lenses of the rabbit, calf, pig, and man. They employed the method of Schild and Maurer, which consisted in the analysis of paper electrophoretic diagrams for P^{32} with a Müller-Geiger counter. The electrophoretic diagram was characterized by three maxima: The first maximum corresponded to the concentration of radioactive inorganic PO_4 ions; the third peak seemed to indicate the P^{32} incorporated in ATP; the analysis and identification of the second maximum met with difficulties —it suggested P^{32} in a group of not readily hydrolyzable phosphate fractions. The uptake of P^{32} in the various phosphate fractions depended greatly on the age of the animal. The authors considered the possibility that in old animals the reduced exchange of P^{32} was caused by a reduced uptake in the inorganic phosphate and the ATP fractions, whereas the not readily hydrolyzable phosphate seemed to take up P^{32} at an increased rate. In an additional study, Müller and Kleifeld [74] presented evidence that the transfer which governs the uptake of environmental P^{32} into the various phosphate fractions of the lens is seated in the capsule epithelium system.

The removal of the posterior half of the capsule did not interfere with exchange of P^{32}, in contrast to the marked decrease of this exchange when the anterior part of the lens capsule and the lens epithelium were removed. The concept of Kinsey and Nordmann of the importance of the lens epithelium as the source of energy for the lens metabolism and the results of the examinations of Palm thus appear to be confirmed by these investigations. From experiments in which he studied the influence of the respiratory activity of the lens on the oxygen content of the aqueous humor, Bonavolonta [75] obtained the following results: The aqueous humor contained 2.76 vol. % of oxygen in normal eyes; when cataract had been produced by massage, the value increased to about twice this figure; the respiratory activity of the lens with massage cataract was reduced to minimal values, and its average oxygen quotient was —0.072, as compared with the normal lens average oxygen quotient of —0.30. In a study on glycolysis in the lens affected with naphthalene cataract, Nordmann, Zimmer, and Mandel [76] observed in a small series an increased production of carbon dioxide accompanied by a decreased Pasteur effect, a change which is characteristic for the metabolism of any injured tissue. In a similar study, Nordmann and Mandel [77] found an increase of glucose consumption prior to the appearance of the lens opacities; the glucose consumption reverted to normal after the onset of the cataractous process. Intermediary products of the carbohydrate metabolism were not changed during the naphthalene poisoning. The authors assumed, therefore, that carbohydrate metabolism must be disturbed at the onset of the toxic effect of naphthalene.

A brief report of an interesting study by the same authors [78] is concerned with the biochemistry of the rat lens with a galactose-rich diet and during alloxan diabetes. The decrease of ATP was found in lenses of rats with partial opacities produced by galactose-rich diet or by alloxan. The authors feel that this reduction in available energy precedes the development of the opacity. In the paper no mention is made of the accurate control of the age of the animals, and, further, only averages of the many experiments are given without standard variations. It is hoped that a more extensive publication will follow on this subject, which seems to be of great importance. It has been shown previously by Patterson that the formation of diabetic cataract depends on a high glucose level in the blood, in a way similar to that observed in experiments with galactose and xylose. In a recent study, Patterson [79] described the synergistic action of galactose and glucose in producing lenticular opacities in rats and thus suggested a similar mode of action of the two carbohydrates. Experimental evidence indicated that the toxic state, that is, a cellular metabolic deficiency, rather than an osmotic effect, was responsible for the development of cataract. Neither ascorbic acid nor phosphate influenced the development of the lens opacity. In a small number of experiments in which animals on galactose diet were intermittently placed on a normal diet, cataracts did not develop. Proper supplement of normal diet seemed, then, to correct the metabolic deficiency at a time when the cellular absorption mechanisms were not blocked by a high sugar level. In the opinion of this reviewer, more extensive studies are necessary to substantiate conclusions on this important point, since there are great variations in the development of galactose cataracts, even under identical experimental conditions. Inoue [80] states that the combined administration of ascorbic acid, riboflavin, and KCl not only impeded the development of experimental diabetic cataract but also reduced previously developed opacities of the lens.

After a brief review and discussion of the literature on the penetration of various substances into the eye, Beauvieux, Blanquet, and Maraud [81] report observations on the distribution of I^{131} in the rabbit following the instillation of the labeled compound in the conjunctiva sac. In contrast to early reports on systemic administration of radioiodine, the lens seemed to take up traces of the isotope. Although the technique is not given in detail, the considerable number of experiments would indicate that the contamination of the lens digest with aqueous humor was not the cause of the traces of iodine in the samples. The concentrations determined in other structures are in agreement with those of previous workers. The radioactivity of lenses with experimentally induced traumatic cataract did not differ from that of the normal lenses under the conditions of the experiments. It is difficult to reconcile these findings with those of other investigators who, with the use of analytical methods and autoradiography, showed a marked increase of the radioactive tracer in lenses with radiation-induced cataract.

Burg and Nordmann [82] determined cryoscopically and with a thermocouple a freezing-point depression of 0.514 degree (C.) in homogenates of the calf lens. Despite the margin of error of the method, they conclude that the lens is isotonic with aqueous humor and vitreous.

Phase contrast microscopy of the fresh ox and calf lens epithelium produced, according to Böke,[83] a great variety of cytological pictures which could hardly be compared with the regularly observed structures in fixed preparations. No cell membranes could be observed, but such membranes became visible by exposures to hypotonic and hypertonic solutions or to fixatives. No true intracellular bridges were seen, and only occasionally a few fibers interconnected adjacent cellular elements. Supravital staining with Janus green made visible numerous round mitochondria. A Golgi apparatus could not be demonstrated.

VITREOUS HUMOR

Rossi,[84] investigating the structure of the vitreous body by means of phase microscopy, reported unexpected results. The controversial interpretations of the microscopic picture of the vitreous on fixed globes, and of the observations obtained by the use of ultramicroscopy and slit-lamp biomicroscopy, have been discussed and reinvestigated by recent workers by means of phase microscopy, electron microscopy and x-ray diffraction. There was principal agreement in the results of these workers as to the presence of fibrous elements of various sizes, shapes, and patterns in the fresh vitreous of several species. In the present study, in which he used the technique of Bembridge, Rossi limited his investigation mainly to the rabbit's vitreous, which he subjected to phase microscopy immediately after the death of the animals, after storage of the vitreous preparations for two to eight hours at 2 C. and after enucleation, six to eight hours after death. Although the number of experiments is not given, the author mentioned that his experiments were repeated many times. In fresh, untreated samples he was unable to detect fibrous structures but observed the appearance of fibrils from 40 to 50 minutes after the eye had been opened and the vitreous fluid had been allowed to escape. An irregular fibrillar network became visible also as a postmortal change. Similar, but not identical, microscopic structures were observed after treatment of the preparation with various fixatives and were explained as the precipitation of the protein content by the chemical agents. Moreover, Rossi stated that he was unable to identify fibrous structure in the fresh,

untreated vitreous of the human eye with this technique. In the opinion of the author, these results suggest that in previous work zonular fibers were mistaken for vitreous elements, and fibrous elements may have been formed through an interaction of hyaluronic acid and the residual protein, as a result of variations in the pH and other physical factors. In view of the limitations and pitfalls of phase microscopy, it will certainly be necessary to wait for confirmative reports before changing our present concept of the structure of the vitreous.

Malatesta [85] studied free amino acids in the aqueous humor and the vitreous humor, using the technique of paper chromatography which he had described in a previous paper.[86] The results do not lend themselves to a short abstract, but it should be noted that in the vitreous fluid the concentration of the nine identified amino acids was lower than in the aqueous humor and that five of the amino acids found in small amounts in the aqueous humor were absent in the vitreous fluid. In a further study,[87] Malatesta compared the free amino acid contents of blood, aqueous humor, vitreous humor, and lens of steer eyes. Phosphocolamine, tyrosine, beta-alanine, phenylalanine, and proline could be demonstrated only in the blood. Lysine, arginine, and alpha-aminobutyric acid were found in small quantities in blood and aqueous humor. Cagianut and Wunderly [88] analyzed the proteins of the condensed vitreous body of four human eyes by means of paper electrophoresis and report an apparently moderate increase of the albumin fraction in eyes which had a high intraocular pressure. The quantitation on a limited number of samples of the very small globulin subfractions with the method used does not seem to this reviewer accurate enough to permit any conclusions.

A review by Grignolo [89] of the present state of our knowledge of the structure of the vitreous body should be mentioned here, as it covers the current information on the chemical components of the vitreous body, notably the characteristics of the residual protein and hyaluronic acid. He emphasizes that neither the chemical composition of the residual protein nor the state of aggregation of hyaluronic acid and its relation to the fibrous elements has been clarified up to the present. A short review of the biochemistry of the vitreous is published by Desvignes and Schapira.[90]

RETINA

In an extensive investigation, Brattgård [91] studied the influence of adequate light stimuli on the growth of the ganglion cells in the rabbit retina and the development of chemical constituents of these cell elements. The cell mass was determined by x-ray microradiography, according to the method of Engström and Lindström and elaboration of this technique by Hydén. For the quantitative analysis of the nucleic acids of individual cells, the authors used ultraviolet spectrophotometry. A considerable increase of the nucleoprotein fraction was noted in animals 10 weeks of age as compared with those 11 days old. In adult nerve cells, when the degree of stimulation was varied, the quantities of nucleoprotein fractions changed appreciably. Retinal nerve cells deprived of stimulation for three days showed a tenfold decrease in the content of nucleoproteins; this content increased after adequate light stimulation. Ten-week-old animals which had been exposed to adequate stimuli had a protein fraction of 0.31×10^{-9} mg. per cubic micron and a nucleoprotein fraction of 0.47×10^{-9} mg. per cubic micron. Animals of this age group which had been kept in total darkness from birth had a protein fraction of 0.16×10^{-9} mg. per cubic micron. From the determination of cell mass, it was concluded that the retinal

ganglion cells surpass in total dry weight other types of nerve cells. What is termed a third growth period of these nerve cells seems to depend on adequate postnatal stimulation. According to the author, the formation of pentose nucleoproteins, which depends on adequate stimulation, precedes the increase in the protein fraction in the development after birth. When stimulation was inadequate during early postnatal life, nerve cells developed incompletely, and their metabolism and chemical composition were disturbed. Sano [92] measured chemically the acid and fat-soluble phosphorus of frog retina, as well as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) phosphorus, which were extracted by the Schneider and the Schmidt and Thannhauser methods, respectively. The amount of the nucleic acids seemed to be greater in the light- than in the dark-adapted retina. The ratio DNA : RNA was in the range 2.8 to 5.2. In the eye of the developing chick embryo the ratio was 0.98 on the 9th day and increased gradually to 16.6 on the 18th day of incubation. Only traces of these nucleic acids could be demonstrated in the vitreous, lens, and choroid of cattle and rabbits. It might be of interest to mention that Ehrlich and Dische, in a similar study, did not observe any influence of the state of adaptation on the content of nucleic acids in the rabbit retina. Postmortal changes in nucleic acid content of the retina were described by Ichikawa.[93] He incubated mouse heads at 20 to 22 C. for from 30 minutes to 48 hours after death, then dry-froze the eyes according to the technique of Altmann and Gersh, and stained sections with histochemical methods for ribonuclease and deoxyribonuclease. From the disappearance and disintegration rates of the two nucleic acids, it was concluded that the ribonucleic acid of the inner limbs of the neuroepithelium was unstable and might be concerned with energy changes associated with vision. It is difficult to evaluate the biological significance of these results if one considers the unphysiological conditions under which these changes were observed.

Oguchi [94] studied the distribution of plasmalogen in the retina of frogs by means of Schiff's fuchsin reaction. The presence of this substance was demonstrated in the pigment epithelium and in the outer and inner limbs of the visual cells, especially the former; the fiber layers also took up the stain. No differences were noted in the light- and dark-adapted states. Yamamoto [95] isolated amylase from rabbit and chick retinae; with this retina amylase it was possible to hydrolyze the polysaccharides contained in the inner segment of the visual elements. The old concept that glycolysis in the retina is similar to that in the body muscles was confirmed. In a histochemical study on the retinae of frog, snake, and chick eyes, Yoshizawa [96] found that the cone myoids contained the most glycogen, indicating that glycogen is stored there to supply energy for the regeneration of visual purple. Dark adaptation reduced the glycogen content, especially in rod retinae. Potassium cyanide and monoiodoacetic acid prevented the loss of glycogen during dark adaptation. Kimura [97] described a corresponding distribution of mitochondria and glycogen in the retina of the rabbit's eye. Okawa [98] demonstrated histochemically the presence of lecithin, cephalin, and sphingomyelin, as well as some other fatty substances, in frog retinae. The amount of these phosphatides decreased during hibernation and after administration of KCN and the sodium salt of cholic acid.

Kornblueth and co-workers [99] studied the influence of variations in chemical composition of the environment on the glucose utilization of the rat retina. In confirmation of old data obtained on other tissues, the authors established that glucose was better oxidized by the retina in a medium of rat or human serum than

in Krebs-Ringer phosphate solution. In Krebs-Ringer bicarbonate buffer, however, glucose utilization reached the same levels as in the rat serum. Addition of organic substrates to the Krebs-Ringer phosphate solution markedly enhanced the glucose utilization, especially when pyruvate, fumarate, and glutamate were used together. Removal of calcium from the serum substitute of Krebs and the replacement of sodium by potassium in this medium increased the glucose utilization by the retina. This function was abolished when the tissue was disrupted and homogenated by grinding, an observation which is in agreement with general experience. In a second study,[100] Kornblueth and associates investigated the effects of hormones and hormonal deficiency states on the glucose utilization of the rat retina. Differences occasionally observed were not considered significant. Their findings indicated that glucose uptake by the rat retina was not influenced by thyrotoxicosis; thyroidectomy; treatment with propylthiouracil; severe hypoglycemia; diabetes; administration of epinephrine, arterenol, desoxycorticosterone, or anterior pituitary hormone extract, or hypophysectomy. This independence of retinal glucose utilization from hormones and hormonal deficiency states is a unique behavior in view of the alteration of this function in other tissues under conditions similar to those of the experiment. Since carbohydrates provide the main source of energy for retinal metabolism, Kornblueth and Yardeni-Yaron [101] undertook a study on the glucose utilization of the rat retina under a variety of physiological and pathological conditions. The influence of age, dark adaptation, light, elevated body temperature, and various diets on this function of the retina was investigated. It was found that none of these factors, including prolonged starvation, protein starvation, and vitamin A and vitamin B_1 deficiencies, produced differences in the glucose uptake of the retina. Only the rise of body temperature brought about by injections of amphetamine was followed by a change, that is, a decrease of glucose uptake, probably a sign of a specific depressing action. According to Sugita,[102] dark-adapted retina of the frog utilized more oxygen than the light-adapted eye; this did not hold true for phosphorus.

Monophosphoesterase was found by Majima [103] almost exclusively in the retina and uvea of steer eyes, whereas most of the adenosinetriphosphatase activity appeared to be localized in the retina. In frog eyes, acid phosphatase increased with light adaptation. In the eyes of chick embryos, acid phosphatase and adenosinetriphosphatase increased about the 12th day and alkaline phosphatase about the 18th day of incubation. Lenti and Cafiero [104] isolated an enzyme preparation from the calf retina with ammonium sulfate. This preparation acted strongly on inosine-5-phosphoric acid and adenosine-5-phosphoric acid, but weakly on adenosine-2-phosphoric acid, adenosine-3-phosphoric acid, and diphosphopyridine nucleotides. Boric acid inhibited the activity of the adenosine-5-phosphatase. Tests were made by Hayano [105] for the presence of acid and alkaline phosphatase in the mammalian retina of various species (calf, rabbit, guinea pig, chicken, and rat), using glycerophosphate, deoxyribonucleic acid, ribonucleic acid, and adenosinetriphosphate as substrates. The inner segments of the visual cell layer stained more deeply in the light-adapted retina than in the dark-adapted state. In histochemical studies on the retina, Pau [106] employed the redox indicators triphenyltetrazolium chloride (TTC) and *p*-phenylendiamine and observed a strong cytochrome-cytochrome oxidase reaction in the nuclei of the neuroepithelium and a maximal TTC reaction near the inner surface of the retina and around the retinal vessels. Also

strongly stained was the nerve fiber layer. This distribution of the products of the tested reactions indicates the location of dehydrogenases, ascorbic acid, and glutathione in the inner layers of the retina and of the cytochrome-cytochrome oxidase predominantly in the outer layers of the retina. Koelle's histochemical technique for the identification of cholinesterase in tissue was applied by Francis [107] to the retina of the pig, sheep, rabbit, rat, guinea pig, pigeon, and frog. However, the author did not use Koelle's later modification to differentiate the specific enzyme from the nonspecific. In most instances considerable quantities of the enzyme appeared to exist only in the region of the internal synapses. Sheep retinae showed a positive reaction also in the area of the external synapses. Traces of activity were demonstrated in some bipolar cells in sheep and rabbit retinae.

Shuichi [108] studied the influence of adrenal hormones on the metabolism of the retina one, two, and four weeks after their injection. After one week a small dose of epinephrine increased oxygen consumption, while large doses decreased this function. Considerable increases in aerobic glycolysis persisted for as long as one month after small doses of the pyrocatechol amine, whereas large doses were without effect. Oxygen consumption and aerobic glycolysis decreased markedly after injections of desoxycorticosterone acetate (DOCA). Similar results were observed when cortisone was used. Since the abstract did not contain sufficient information to allow statistical analysis, the value of the study cannot be appraised. Supplementing his previous investigations, Noell [109] reported on the ophthalmological, histological, and electroretinographic changes induced by intravenous injections of sodium acetate and sodium iodate. The retinal lesions occurring after administration of these metabolic poisons were observed in monkeys, cats, and albino rabbits. Iodoacetate caused a widespread disappearance of the rod cells within two to four weeks after injection, while the cone cells appeared to be more resistant to the metabolic poison. The author pointed to the great similarity of the experimentally induced damage and the sequence of changes described in the development of retinitis pigmentosa. In his opinion, an impairment of the glycolytic process by the action of iodoacetate is the principal cause of the degenerative changes in retinitis pigmentosa. Sodium iodate affected the rod cell population in a slightly different manner and damaged the pigment epithelium more severely than did iodoacetate. In the discussion of his paper, several objections were raised against Noell's interpretation of these experiments and the comparability of the experimental lesion with the process of retinitis pigmentosa. Metabolic and histological studies on the retinae of rabbits were also carried out by de Berardinis [110] after the intravenous injection of 30 to 40 mg. of iodoacetate per kilogram of body weight. He observed a decrease of the pupillary reaction to light and, ophthalmoscopically, the development of retinal edema with the characteristic pigmentary degeneration, as described by Noell and others. Histologically, it was noted that destruction of the neuroepithelium preceded more advanced stages of atrophy of the retina. Thirty days after the injection, retinal glycolysis was reduced, whereas in the vitreous body the glucose level increased and the lactic acid content decreased. These results are interpreted as indicating a specific inhibition of glycolysis by iodoacetate. A similar opinion, expressed by Noell, was questioned by Dische, who considered it invalid to attribute specific effects to a metabolic poison when it is used in such high concentrations. An additional description of degeneration of the outer retina in rabbits induced by intravenous injection of sodium monoiodoacetate was given by Karli.[111]

VARIOUS OCULAR FLUIDS AND TISSUES

In the report of his studies on the preocular film, Vidal [112] discussed the possible transformation of lipotropic factors into phospholipids, fatty acid, oleic acid, free cholesterol, esters of cholesterol, and neutral fats, which in pathological conditions are found in this fluid. The similarities of the preocular film and the epidermic emulsion are briefly considered by Vidal and Mom,[113] but no original results are reported.

In the monograph of Junnola [114] on the properties of human lacrimal secretion, two chapters deal with the physicochemical examination of tear fluid, and only this part will be reviewed here. By means of a nephelometric technique, the protein content in samples of tear fluid was determined in a young and in an older age group. The respective figures were 378 and 345 mg. per 100 cc. In view of the great variations of the values in individual samples (from 136 to 592 mg. per 100 cc.) and the size of the series (30 tests), this difference cannot be considered statistically valid. The protein content was scarcely influenced by instillation of atropine, scopolamine, and Optochin. The question of a relation between the type and variety of several conjunctival and corneal diseases and the protein content remained obscure, although a decrease of the protein value was suggested in examination of eyes with advanced forms of serpiginous ulcer. In this connection, the author points to an observation that the protein content seemed to fall with an increase of lacrimal secretion. The protein level in tears was determined by Balik and Hradecky,[115] using the nesslerization process. One hundred samples of tears were taken from 25 normal persons. The authors determined the per cent of nitrogen in samples of mucin (4.5%) and calculated the amount of mucin in the tears. They arrived at the figure of 30 mg. as the amount in normal tear secretion for five minutes. Since titration methods for the determination of chlorides in tears are not suitable, in view of the small quantities involved, Balik [116] applied polarographic determinations for this purpose. The small protein content of tears was not a disturbing factor. Balik measured an average concentration of 1.007 gm. of sodium chloride per 100 cc. in a medium quantity of the secretion, indicating that the level of the chlorides is about the same as that in the blood serum but is adjusted above or below the average value according to local demands. Increased secretion was accompanied first by a slight rise in chloride concentration and later by its fall. The initial rise in concentration may be attributable to the activity of the cell elements of both secretory systems and the solubility of the mucin. These data on osmotic pressure of the lacrimal fluid confirm the results reported by Revol, Nouvel, and Jaumald,[117] who used freezing point determinations and found that the lacrimal fluid is isotonic with serum. The value of 14 gm. per liter, accepted for the sodium chloride content, thus was not confirmed in the material which the French authors used. Similarly, investigations on the conductivity and vapor pressure of lacrimal fluid by Pendersen-Bjergaard and Smidt [118] indicated a constant osmotic pressure of the secretion, almost equal to 0.9% solution of sodium chloride. The pH values ranged around 7.4.

Using a modified Gomori method, Allen and Friedenwald [118a] carried out an extensive histochemical investigation of a number of specific phosphatases; namely, the two phosphatases attacking polyglycol monophosphates (one, A, inactivated and the other, B, activated by Mg ions); two enzymes splitting adenosinetriphos-

phate with a pH optimum of 9.9 and 8.25, respectively, which the authors assume to be pyrophosphatases, and enzymes specifically directed against fructose-1,6-diphosphate, creatine phosphate, and adenosine-3- and 5-monophosphate. There was no indication of the presence of the nonspecific alkaline phosphatase in ocular tissues. The presence and the localization of these enzymes in the individual ocular tissues was determined. The enzyme splitting hexosdiphosphate and the two enzymes splitting adenosinetriphosphate were found in all investigated tissues (lens, iris, ciliary body, cornea, conjunctiva, sclera, choroid, retina, pigment epithelium, optic nerve). Enzyme A was completely absent in all tissues, and the enzyme splitting creatine phosphate was found only in the epithelium of the conjunctiva after incubation of 24 hours. Of particular interest is the fact that the fructose diphosphate in the lens appeared to be localized in the epithelium and in the neighborhood of the cellular membrane of the lens fibers. The presence of the enzymes in the nuclei, which was observed under certain conditions, is shown by the authors to be an artifact.

DeRoetth [119] examined the oxygen uptake of dissected ciliary processes of a great number of steer eyes in air and oxygen and in various suspension media. The QO_2 rose from 2 to 4 when the gas phase was changed from air to pure oxygen. In contrast to other tissues, various metabolites influenced the oxygen consumption of the ciliary process only in the experiments with pure oxygen. The addition of acetylcholine and physostigmine resulted in a considerable increase of the oxygen uptake, while pilocarpine and epinephrine were almost ineffective. Dinitrophenol in low concentrations caused an increase, in higher concentrations a depression, of oxygen utilization. A depressing effect of cyanide was demonstrated when either air or oxygen was used as the gas phase. A moderate and somewhat equivocal influence on oxygen consumption was observed when metabolites, such as sodium succinate, malonate, pyruvate, fumarate, and glutamate, were added to the fluid medium. Angenent and Koelle,[120] in a study of a possible enzymatic basis for the differential action of mydriatics on light and dark irides, demonstrated that the dopa-oxidase system of the anterior uvea of pigmented rabbits, but not of albino rabbits, can cause a high rate of oxidation of epinephrine in the presence of dopa (dihydroxyphenylalanine). On the other hand, pigmented and albino rabbits did not differ with respect to monoamine oxidase, cytochrome oxidase, cholinesterase, or reducing substances. The relative ineffectiveness of mydriatics on dark irides might thus be explained by the rapid destruction of the chemical mediator of adrenergic fibers by dopa-oxidase. The depressed synthetic impulses could then not compete sufficiently in counterbalancing the action of the cholinergically innervated sphincter muscle.

Koelle and co-workers,[121] by a newly modified technique, were able to distinguish histochemically the nonspecific and the specific cholinesterase in tissues of the cat's eye. The specifically acting enzyme was located predominantly in two bands of the retina, one in the innermost region of the inner nuclear layer and one in the inner part of the inner plexiform layer. In thin sections, the elements which were stained in the outer plexiform layer consisted of cell bodies, identified as amacrine cells. Sections through the optic nerve showed definite activity in the trabeculae between the nonstained visual nerve fiber bundles. The authors assumed that these stainable fibers were autonomic. In the anterior segment, the ciliary and iris sphincter muscles

and their associated nerve fibers stained deeply for specific cholinesterase activity but seemed practically devoid of nonspecific cholinesterase. Rickenbacher [122] used the methyl green-pyronine and the Feulgen technique to study the distribution of ribonucleic acid and deoxyribonucleic acid in individual cells of amphibia and chicks. The second part of the study concerned the behavior of the nucleic acids in eye tissues of these species during development. RNA was present mostly at the surface of the nucleus, in the cytoplasm, and in the nucleolus. It decreased during mitosis in amphibia. During the development of the eye the RNA increased, but it decreased at the period of differentiation. With respect to DNA, the results were less precise and require further investigation. Weitzel and Fretzdorff,[123] in an extensive study, compared the zinc content of the lens, vitreous, retina, and choroid of horse, deer, ox, calf, pig, wild boar, sheep, goat, rabbit, hare, dog, fox, marten, weasel, polecat, and cat. The lens and vitreous of all species showed a relatively low content of zinc. The choroid was high in zinc in cats and rabbits and showed the highest values in dog, marten, and fox. The zinc content of the choroid of pigmented and that of albino rabbits were of the same magnitude. In a study of the biological significance of the ocular changes due to prolonged deficiency in vitamin E, Corrado [124] observed corneal edema and hypesthesia, interstitial keratitis, uveitis, water clefts and opacifications in the lens and degenerative changes in the choroidal and retinal vessels. Since the majority of these changes were prevalent in mesodermal tissues, Corrado interpreted them as due to the hydrolyzation and depolymerization of hyaluronic acid, which was no longer inhibited by vitamin E. Thus, he considered the vitamin as a factor regulating the enzyme balance of connective tissue and concluded that a deficiency of this vitamin leads to the development of "mesenchymopathies," including the changes noted in the ocular mesenchymal tissues. The influence of an experimentally decreased oxygen supply on various functions of the eye has been studied in the past by several investigators, but most recently interest centers around this problem in the field of aviation medicine. Bietti [125] reports the results of an extensive study in which he produced anoxia by letting human subjects breathe air mixtures with an oxygen content which approximated the oxygen supply at 13,000 to 26,000 ft. (3,940 to 7,880 meters). In addition, relative anoxia of retina and optic nerve was produced by compressing the eyes with a Bailliart ophthalmodynamometer. Diagnostically important depression of several functions of the visual apparatus by hypoxia was paralleled by an improvement of the responses when hyperoxia was induced. This elaborate study is mostly of clinical significance. The relation to the physiological chemistry is obvious and may stimulate new laboratory studies in this field. Such a study was published by Swanljung and Giardini,[126] who found an increase in fluorescein permeability of the blood-aqueous barrier in cats during anoxia.

VISUAL PIGMENTS

SECTION WRITTEN BY RUTH HUBBARD, PH.D., BIOLOGICAL LABORATORIES, HARVARD UNIVERSITY, CAMBRIDGE, MASS.

Synthesis of Visual Pigments in Vitro and in Vivo.—Last year, in this journal,[127] I reviewed at some length recent work on the synthesis of rhodopsin, the photosensitive pigment found in the rods of most vertebrates (except fresh-water fishes), and of iodopsin, the cone pigment of the chicken retina. These studies have also

been reviewed by Wald,[128] together with experiments on the synthesis of porphyropsin, the rod pigment of fresh-water fishes. All three pigments are synthesized by the combination of one of two types of opsin, derived from rods or cones, respectively, with a specific cis isomer of retinene$_1$ or retinene$_2$. These relations are summarized in the accompanying Table. The combination of rod opsin with retinene$_1$ yields rhodopsin; cone opsin and retinene$_1$ form iodopsin, and rod opsin and retinene$_2$, porphyropsin. The same cis isomer of retinene is required in each case. In addition, Wald, Brown, and Smith[129] have now synthesized a fourth pigment, cyanopsin, by combining cone opsin with cis retinene$_2$. The absorption maximum of this pigment is at 620 mμ (Table). The shape and position of its absorption spectrum agree with electrophysiological measurements by Granit on photopic (cone) vision in the tench and the tortoise. The tench, a fresh-water fish, is known to contain vitamin A_2 in its retina, and Wald has also found vitamin A_2 in two species of turtle. Cone vision in vitamin-A_2 animals therefore appears to be mediated by cyanopsin. It should be noted that cyanopsin extends the range of absorption spectra of visual pigments into the red. This raises the possibility of its role as a "red receptor" in color vision.

Some of the properties of five stereoisomers of retinene$_1$ have been described.[130] The five known isomers are all-trans; three mono-cis forms—neoretinenes a and b

Composition and Spectral Characteristics of Visual Pigments

Pigment	Protein	Cis Retinene	Absorption Maximum, Mμ
Rhodopsin	Rod opsin	Retinene$_1$	500
Porphyropsin	Rod opsin	Retinene$_2$	522
Iodopsin	Cone opsin	Retinene$_1$	562
Cyanopsin	Cone opsin	Retinene$_2$	620

and isoretinene a—and one di-cis isomer—isoretinene b. Neoretinene b combines with opsin to yield rhodopsin; isoretinene a produces a rhodopsin analogue, called isorhodopsin. The other isomers do not react with opsin. Rhodopsin synthesis can be used as a tool in the analysis of mixtures of retinene isomers, as the combination with opsin allows one to detect 1 γ or less of neoretinene b or isoretinene a, even in the presence of a large excess of the other isomers.

Collins, Green, and Morton,[131] have extended their studies on the synthesis of rhodopsin in homogenates of retinas from frog and rat. They achieve the optimum rate and yield of synthesis in the frog when the tissues are incubated in the dark in the presence of diphosphopyridinenucleotide (DPN; cozymase), nicotinamide, cytochrome c, all-trans vitamin A, ATP, and Mg^{++}. With rat retinas, supplementation only with vitamin A is required. The role of the various components in the frog system is obscure. It is clear, however, that both systems must be capable of converting all-trans vitamin A or retinene to the neo b isomer, as all-trans vitamin A was effective in enhancing rhodopsin synthesis.[127]

Hanaoka[132] has continued his experiments on the effect of melanophore hormone on rhodopsin synthesis in vitro and in vivo. He claims that the hormone increases the rate and yield of synthesis in both instances, but it is very hard to know how

to interpret his experiments. He works with extremely dilute solutions (optical densities all below 0.1, and some as low as 0.005), so that the changes in optical density which he measures and takes as evidence of rhodopsin synthesis are very small (an increase of 0.003, from 0.0055 to 0.0085, is considered significant), and he fails to comment on such extraordinary results as a regeneration of rhodopsin to a value 1.53 times that of the dark-adapted control (optical densities of 0.013 and 0.020, respectively). All in all, I am not yet convinced that he is really measuring an effect of the hormone in vivo or in vitro.

Hagins and Rushton [133] have developed an interesting technique for observing the course of rhodopsin synthesis in the eye of the decerebrate albino rabbit. It is based on the following principle: When plane-polarized light is shone into the albino eye, an appreciable fraction is reflected back. Light that is reflected at the lens and corneal surfaces retains its polarization, but the rest is reflected diffusely from the back of the eye and depolarized. If the reflected light is viewed through a Polaroid crossed with the plane of the incident beam, only light is transmitted which has passed twice through the retina, and hence twice through the rhodopsin of the rods. One can therefore measure the change in rhodopsin concentration in the lining retina during light and dark adaptation. Rushton,[134] with Brindley, has done similar experiments with unpolarized light. Both sets of measurements show that after light adaptation the density of rhodopsin in the dark rises linearly for about an hour and then levels off very suddenly. The total density change, measured in blue-green light, is about 0.2 log unit, implying that about 35% of the light is absorbed in a single passage through the retina. In both sets of experiments the authors find that a light 100,000 times the human threshold does not appreciably affect the measured density of rhodopsin; a light 10 times as bright causes fairly rapid bleaching.

Similar measurements have been made by Weale [135] in the cat's eye. He finds that the absorption maximum of cat rhodopsin in situ lies at 497 mμ, in good agreement with rhodopsin extracted from the retinae of rats and cattle, but about 5 mμ lower than that of frog rhodopsin. The maximum density of pigment in the retina is about 0.1 log unit and is achieved about 30 minutes after the beginning of dark adaptation. In a few cats,[136] he has also found another pigment, with a maximum at 565 mμ (iodopsin?), which regenerates completely within about two minutes after light adaptation. This behavior is strikingly parallel to the relative rates of synthesis of rhodopsin and iodopsin in solution.[128]

Distribution of Visual Pigments.—Kampa [137] has examined the visual pigments from dark-adapted retinae of three marine (plaice, gurnard, and pollack) and two fresh-water fishes (trout and tench) to check an earlier report that five species of fish have as many different visual pigments. On the contrary, she finds that the tench has porphyropsin (maximum absorption at 520 mμ) in its rods, the trout has a mixture of rhodopsin and porphyropsin, and the three types of marine fish have rhodopsin alone.

Collins and co-workers [138] have examined the visual pigments of the tadpoles of Rana temporaria and Rana esculenta and find only rhodopsin in their retinae. This is in contrast to tadpoles of Rana catesbiana, whose visual pigments which in the course of metamorphosis change from porphyropsin over a series of mixtures of porphyropsin and rhodopsin, to rhodopsin alone in the adult frog.[139] Collins and

colleagues, unfortunately, have not analyzed the retinae for vitamins A_1 and A_2. The spectra of the visual pigments which they publish do not exclude the possibility that their extracts contained an admixture of porphyropsin. They venture some interesting speculations on the role of vitamins A_1 and A_2 in evolution and the possible origin of vitamin A_2 from β-carotene or other vitamin-A precursors.

Crescitelli and Dartnall [140] have extracted rhodopsin from a dark-adapted human retina. Its absorption maximum lies at 497 $\pm$ 2 mμ, and the shape of the absorption band agrees well with the spectral sensitivity of human scotopic (rod) vision. They calculate the optical density of rhodopsin in the retina to be about 0.016. This is considerably lower than the values cited above for the cat and the albino rabbit.

Dartnall [141] has observed that the absorption spectra of rhodopsins from various animals, as well as those of porphyropsin, iodopsin, and his "visual pigment 467," from the tench,[127] have the same shape if plotted against frequency rather than against wave length as the abscissa. From this fact, he concludes that all visual pigments have absorption spectra of the same shape, and he has constructed a nomogram which allows one to derive the absorption spectrum of any hypothetical visual pigment if one knows its wave length maximum. He uses such spectra to compare with visibility curves derived from sensory data in animals from which photosensitive pigments have not yet been extracted. It seems to me, however, that he overstates the case for the nomogram when he interprets the cone response curves of the frog (wave length maximum at 560 mμ) and the tench (maximum at 610 mμ) as follows:

> The curves in fig. 3 are the absorption spectra, calculated from the nomogram of fig. 1, of hypothetical visual pigments having maxima at 560 mμ and 610 mμ. Both these curves are too broad to fit the sensitivity data. . . . Thus the spectral sensitivity curves . . . cannot be interpreted in terms of single visual pigments.

This may be so, but the poor fit may just as well imply that the theory underlying the nomogram chart is not infallible. The recent synthesis of cyanopsin has, in fact, yielded a pigment which fits remarkably well with the cone sensitivity curve of the tench.[129]

Structure and Molecular Extinction of the Rhodopsin Chromophore.—Collins [142] has done an interesting experiment concerning the attachment of retinene to opsin in rhodopsin. In bleached solutions of rhodopsin, retinene is found combined with amino groups on opsin. (This combined form of retinene has been called "indicator yellow.") This situation could arise in one of two ways: Either (*a*) retinene is attached to amino groups in rhodopsin and the bond remains intact during bleaching, or (*b*) retinene is bound in some other way in rhodopsin, but on bleaching attaches itself to free amino groups on opsin. Collins has distinguished between these possibilities by bleaching rhodopsin, which has had its free amino groups masked with formaldehyde. In situation *a* bleaching should still release retinene as the amino complex; but in the case of *b* retinene will be uncombined because all the amino groups are already covered by formaldehyde. Collins' experiment shows clearly that retinene also under these circumstances exists as the amino complex. He therefore believes that the rhodopsin chromophore contains retinene attached to an amino group on opsin. As supporting evidence, he also shows that the compound of retinene with methylamine yields a rhodopsin-like spectrum upon treatment with antimony chloride.

Wald and Brown [143] have measured the molar extinction coefficient of rhodopsin in a new and more reliable way. They have avoided many of the technical difficulties encountered in previous determinations by measuring the extinction of all-trans retinene oxime formed on bleaching rhodopsin in the presence of a large excess of hydroxylamine. The extinction coefficient of the oxime can be measured with much greater accuracy than the extinction coefficient of the amino complexes which retinene otherwise forms with opsin (preceding paragraph). They find that the extinction of cattle rhodopsin per mole of retinene is 40,600 sq. cm. It has recently been shown that cattle rhodopsin contains only one retinene unit per molecule.[144] This is therefore also the molar extinction coefficient of rhodopsin. A number of years ago, Schneider, Goodeve, and Lythgoe [145] evaluated the product of the extinction coefficient and the quantum efficiency for bleaching rhodopsin to be 23,700 sq. cm. per mole. Considered together with the new data of Wald and Brown, this implies a quantum efficiency of bleaching of 0.58. The authors suggest that this is due to partial resynthesis of rhodopsin from the intermediates of bleaching.

Ultrastructure of the Rods and Cones.—Wald [146] had published a number of photomicrographs of frog rod outer limbs and reviewed what was known about their functional organization before Sjöstrand's † beautiful analysis of rod and cone structure with the electron microscope. Sjöstrand's studies reveal an amazing degree of regularity in the structure of these photoreceptors. In the guinea pig, the rod outer limb consists of a regular stack of membranes, 1,400 in all, which are connected in pairs to form "double membrane discs." The thickness of each membrane is 30 A,‡ and that of the entire disc, about 140 A. The 700 discs are stacked at a density of about 40 discs per micron. The total membrane surface per rod is about 4,500 sq. μ. The rod outer limb of the perch is organized along similar lines. Here the membranes are 80 A, and the discs 240 A thick. There are about 31 discs per micron and about 1,400 discs per rod. The total membrane surface is about 4,600 sq. μ per rod. In perch cones, the pattern is similar, but the membranes are much thicker than in the rods (about 170 A) and are not associated in pairs. There are about 33 single membranes per micron and 800 per cone. The total membrane surface is about 4,700 sq. μ per cone.

It may be significant that the membrane surface is about the same in all three receptors. Sjöstrand thinks that the lipids of the rod outer limb (about 40% of the dry weight) are concentrated within the compartment enclosed by the double membrane and that the membrane itself consists of protein.

Each double membrane disc bears an incision, and these are lined up to form a longitudinal fissure in the outer limb, which may contain fibrils connecting it with the inner limb. The inner limb contains the ellipsoid, which seems to consist mostly of mitochondria. These are usually associated with the biosynthetic functions of cells. The apical portion of the inner limb may therefore act as a metabolic center of the rod. The outer and the inner limb each is surrounded by a membrane also along the contiguous surfaces. They are thus entirely separate except for a small bundle of connecting fibrils. In the inner limb, the fibrils establish close connection with the mitochondria and with a single, larger fiber, the

† References 147 and 148.

‡ $1A = 10^{-4}\ \mu = 10^{-8}$ cm.

"inner segment fibril." Sjöstrand thinks that light absorption and excitation probably occur within the membranes of the outer limb, the excitation being transmitted by the fibrils to the inner limb, where the mitochondria may supply the energy for further conduction. This idea, of course, is only speculation, but the remarkable state of organization revealed in Sjöstrand's electron micrographs must tempt even the soberest among us to flights of fancy.

Spectral Sensitivity and Color Vision.—(*a*) Electrophysiological Measurements: Wirth [149] has derived scotopic visibility functions of the cat and albino rabbit from the spectral sensitivity of the electroretinograms. His measurements for the cat agree with those for the human scotopic function and with other electrical and behavioral data obtained with cats. His curve for the albino rabbit, however, is much narrower and shows an enhanced sensitivity in the red. He suggests that the increased red sensitivity may be due to an admixture of cones. The narrowness of the visibility curve is, however, hard to explain. His suggestion that it may be due to a very low concentration of rhodopsin is not supported by Rushton's estimate of the rhodopsin content of the albino rabbit's retina.§

Rushton [150] has identified the retinal "elements" from which Granit has been recording electrical responses as giant ganglion cells both in the cat and in the frog. This implies that Granit's measurements have been made at a level considerably more complex than the receptors. Rushton points out that these animals must therefore sort and condense information received by the receptors already at the retinal level. This is not true of the primate fovea, which sends fibers via the midget bipolar cells directly to the brain. He suggests that this may be the reason why optic nerve records corresponding to our own sensations are more frequently obtained in the king crab, Limulus, whose optic nerve fibers come straight from the receptor cells, than in the frog or cat.

In a discussion of the problem of excitation,[146] Hartline suggests that the electrical response of the receptor should not be considered as the first expression of light absorption, since it exhibits latencies up to several tenths of a second (following a millisecond flash) and starts abruptly as though preceded by a build-up of something else.

Autrum [151] has reviewed some of the electrophysiological literature, particularly in insects. The electroretinogram (ERG) of these animals resembles that of the vertebrate eye in every detail. But whereas man has a flicker fusion frequency of 30 to 40 flashes per second, bees and flies exhibit frequencies up to 300 per second. Autrum suggests that this may be a physiological adaptation to compensate for the large size of the ommatidia in the insect eye, which gives bees only about one-eightieth the spatial resolution of cone vision in man. Their high flicker fusion frequency provides them with a method of temporal discrimination which may enable them to scan the image rapidly in television-projector fashion. This effect is further enhanced by a very rapid course of dark adaptation. The great reactivity is abolished by removal of the optic ganglia, which renders the response of flies and bees more sluggish, and comparable to that of other insects (grasshoppers, dragonfly larvae, etc.).

Ottoson and Svaetichin [152] have started an interesting series of experiments trying to discover by the use of ultramicroelectrodes (about 1 μ diameter) the site

§ References 133 and 134.

of origin of the ERG within the retina. They find that an ERG of the usual type, containing all three normal components, arises in the receptor layer itself (rods and cones). It can be recorded between electrodes one of which is placed on the vitreous surface of the retina, and the other anywhere between the outer limiting membrane and the distal end of the receptors. Dark-adapted eyes (frog) give a large positive deflection in the ERG, but light-adapted eyes show only negative deflection.[153] The authors conclude that the positive component is due to rods and the negative component to cones. Records from within the receptor layer often give only one or the other type of response, suggesting to them that they may be recording from small clumps of receptors containing primarily rods or cones. With even finer electrodes (0.05 μ tip), Svaetichin [154] has observed potentials arising at the level of the cone myoids of isolated fish retinae (bream and perch). There is no significant change of amplitude with the state of cone adaptation. The amplitude of the response, however, varies with the light intensity, a finding which he interprets to mean that the all-or-none law does not hold for the receptors. The data, however, do not force this conclusion, as he does not claim to be recording from single cones. Svaetichin has also examined a number of other visual phenomena. The most challenging experiments involve an attempt to record spectral sensitivity curves from individual cones, or small groups of cones. Svaetichin believes that he can distinguish three main types of cones, with sensitivity maxima at 450, 550, and 600 mμ, respectively (the last with a secondary hump at 650 mμ), in approximate agreement with the three color primaries postulated by the Young-Helmholtz theory of color vision. More experiments are needed to establish this claim, which opens new and fascinating possibilities for exploring the phenomena of color vision.

Donner [155] has studied the spectral sensitivity of the pigeon with Granit's microelectrode technique (tip diameter of about 10 μ), recording from the giant ganglion cells of the retina.[150] His scotopic curve agrees well with the absorption spectrum of rhodopsin. At photopic brightness levels, he finds three or four types of modulators, which he thinks can be combined to give a photopic dominator curve.‖ Both types of photopic response curves are, however, shifted to the red as compared with the spectral responses of the frog. This is presumably due to selective absorption of blue and green light by the cone oil droplets of the avian retina. These droplets lie between the inner and the outer segment and thus filter the light reaching the outer segment. The next year or two will probably show whether it is right to think of the photopic dominator curve as a composite of individual narrow modulater responses. The two cone pigments extracted and synthesized by Wald, Brown, and Smith ¶ both fit the so-called dominator functions reasonably well. It is therefore likely that individual cones can give the dominator response. There may be other cones which give modulator responses. Alternatively, responses from cones containing iodopsin or cyanopsin (either of which has a broad, dominator-like spectrum) may be somehow modified to produce the narrow modulator curves recorded by Granit and Donner.

‖ "Modulator" and "dominator" are terms introduced by Granit to distinguish two types of cone response as recorded electrically from the retinal ganglion cells. "Modulators" respond over a narrow region of wave lengths and therefore exhibit sharply peaked spectral sensitivity curves. "Dominators" exhibit a broad sensitivity curve, as in rod vision.

¶ References 128 and 129.

(*b*) Psychophysiological Measurements: Stiles [156] has published a review of his measurements of the spectral sensitivities of three cone mechanisms—blue, green, and red. These are obtained by studying the effect of selective adaptation with colored lights on the increment threshold ($\triangle$ I) at various wave lengths. His cone mechanisms have maxima at about 440, 550, and 590 mμ, respectively, and have broad (dominator-like) sensitivity curves.

Weale # has measured spectral sensitivity and color discrimination in the fovea and at eccentricities of 10, 15, 25, 45, and 70 degrees. In all these locations the curves exhibit enhanced sensitivities in three spectral regions—orange, green, and blue-violet—suggesting that three principal mechanisms are present and equally active over the entire retina. But wave length descrimination falls off markedly in the peripheral retina. Weale postulates that the loss of color discrimination is due to a convergence in the anatomical and physiological connections at a level behind the primary photoreceptor process. He has also measured the spectral sensitivity of three cone monochromats between 420 and 700 mμ.[159] Their sensitivity functions are somewhat narrower than those for two normal observers, but not strikingly so. Here, too, he concludes that the deficiency in the color-mediating mechanism is located at a higher level than the photoreceptors, since the actual light-absorbing mechanisms seem to be fundamentally similar in all observers.

Reviews.—Geldard's "The Human Senses" [160] includes four chapters on vision. Symposia on the physiology of vision have also been published in the *British Medical Bulletin* and in *Acta physiologica scandinavica.* A number of contributions from both journals are reviewed above.* The fourth Josiah Macy, Jr. conference on the nerve impulse includes a discussion on vision by Wald,[146] with comments by Hartline, Barlow, Nachmansohn, and others. There has also been a review on the biochemistry of vision in *Annual Reviews of Biochemistry* [161] and in *Federation Proceedings.*[128] Wald [162] has also written a review on the metabolic role of vitamin A, particularly in vision.

References 157 and 158.

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Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

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Combined Meeting, Dec. 21, 1953

Malignant Lymphoma with Ocular Involvement. Dr. Isadore Givner.

A woman, married, age 49, presented herself Dec. 10, 1951, with a history of having had acute pancreatitis three months previously, at which time the vision of the left eye was affected. Since then the vision in the right eye had also not been clear.

The right eye showed nongranulomatous uveitis. Vision was still 20/20—.

The left eye was normal except for the vision, which was 20/200, and an elevated mass in the macular area. With it were some subretinal fluid and three smaller lesions below the main one. The lesion could be transilluminated well.

The complete examination of the patient was negative. Subconjunctival injections of cortisone produced no change in the right eye, but the appearance of the left macula was markedly altered. The lesion disappeared, leaving pigmented degenerative areas. Vision improved gradually until on May 16, 1952, it was 20/25—.

The patient was concerned about her right eye and asked for a consultation with Dr. Alan C. Woods. His examination showed no general condition other than a 3+ reaction to one strain (out of 28 strains) of subgroup A of the beta hemolytic streptococci. He advised intravenous desensitization. This was begun June 20, when 0.1 cc. of first strength was given.

The following day styes appeared on the lids of both eyes. One week later a swelling of the left parotid gland occurred. Biopsy showed inflammatory tissue. At this time all the lymph nodes over the body were enlarged. After x-ray treatments the left parotid area returned to normal. As the patient felt that there was some connection between the intravenous vaccine and her general condition, no further intravenous Streptococcus vaccines were given.

On Sept. 28, the patient developed weakness of her left arm, left facial paralysis, and ptosis of the right upper lid, associated with stupor. At operation a brain tumor was found in the left temporoparietal region; the neurological findings must, therefore, have been due to the distant effects of pressure. The undifferentiated malignant growth removed resembled reticulum cell sarcoma. The patient did not do well until given intravenous injections of nitrogen mustard, 8 mg. daily. Remarkable improvement then occurred, and the patient later walked out of the hospital, feeling well.

On Dec. 17, 1952, metastatic lesions occurred in the bulbar conjunctiva of both eyes, as well as in the skin of the chest. Biopsy showed reticulum cell sarcoma.

At this point the question as to whether the Streptococcus vaccine could have hastened the generalized involvement demanded clarification. That the Streptococcus has been linked to lymphosarcoma is attested to by the history of Coley's vaccine. Busch, in 1868, noticed that lymphosarcoma occasionally disappeared if the patient contracted erysipelas. In 1881 Fehleisen discovered the Streptococcus erysipelatis and inoculated human patients with this culture to make lymphosarcoma regress.

William B. Coley, in 1884 at the New York Hospital, noted 10 cases of lymphosarcoma in which the tumor permanently disappeared after the patient acquired erysipelas. In 1891 he tried killed cultures of Str. erysipelatis, but this vaccine was too weak. In 1892 he utilized a fact uncovered by Rogers at the Pasteur Institute, namely, that Bacillus prodigiosus (Serratia marcescens) increased the virulence of other organisms, and he used Coley's mixed toxins of both the Str. erysipelatis and B. prodigiosus.

Bradley L. Coley, his son, today finds that 50% of patients with reticulum cell sarcoma treated with radiation and Coley's vaccine are alive after five years. In a case cited in his book, "Neoplasms of Bone" (page 338), a patient with this condition, who had already had metastases to the spine, scalp, and clavicle, was treated only with Coley's vaccine and was well, 21 years later.

A piece of the skin taken for biopsy in the case presented this evening was placed in the anterior chamber of the eye of a rabbit but did not grow. This lack of growth in malignant lymphoma was also the experience of Dr. Harry S. N. Greene, of Yale University, who initiated this type of experimentation to help in differentiating anaplastic tissue. The tissue did not grow even after the rabbit was given intravenous Streptococcus vaccine of the strain the patient was sensitive to.

Nitrogen mustard again made the patient's lesions disappear. The patient's course was then downhill. The vitreous of the right eye became cloudier. A subconjunctival salmon-colored chemosis developed in the left eye. The patient died May 19, 1953.

Complete autopsy, including examination of both globes, was procured. The vitreous of the right eye showed many inflammatory cells—polymorphonuclear leucocytes, lymphocytes, and plasma cells—but in all serial sections the vitreous in the region of the ciliary body showed well-preserved cells with larger nuclei than in the other cells of the vitreous.

In the left eye a marked subconjunctival infiltration of lymphomatous cells invaded the superficial sclera and extended into the cornea. The macula of the left eye showed subretinal transudate and a marked thickening (six times the normal) of the lamina vitrea, suggestive of a degenerative lesion.

Subsequent skin testing of two other patients with lymphosarcoma (generalized) showed no sensitivity to the vaccine to which the patient in question was sensitive.

Conclusion.—Any relationship that might seem to exist between the injection of the Streptococcus vaccine and the precipitation of the reticulum cell sarcoma was purely coincidental.

Lymphomatous Tumors of the Eye. Dr. John S. McGavic (by invitation) Bryn Mawr, Pa.

This paper was concerned with a follow-up study of 20 of 21 patients with lymphomatous tumors involving the eye and its adnexa. In 1942 a report of these patients was published after an average follow-up of four years. This, the second report, represents a follow-up of 15 years. In each case there was biopsy material from the ocular lesion, as well as from any remote tumor available.

It is to be emphasized that the lymphomatoid diseases are interrelated and may be transmitted from one type to another, with or without leukemia.

Of the 20 patients, 5 are alive today, only 1 having evidence of disease. Five patients died of conditions other than lymphomas, after an average of 15.5 years. Fourteen of the tumors were primary in the region of the eye, and 7 remained localized until 1953 or until death from other causes. The seven patients with tumors primary in the region of the eye which later spread survived an average of 9.8 years, while those with generalized lymphosarcoma before an ocular tumor appeared survived only 4.6 years. The survival rates according to cell types were as follows: lymphocytic cell, 13.6 years; giant follicle, 13.0 years; reticulum cell, 7.2 years.

It was found that the clinical appearance of the eye was the same for those who lived as for those who died. The histologic appearance of the subconjunctival tumors was not reliable for prognostic purposes. In general, the prognosis is better than is generally believed.

DISCUSSION

DR. GEORGE MERRIAM: I wish to emphasize only a few important points and discuss the treatment briefly.

Follow-Up.—One of the outstanding features of this series is the length of the follow-up period. A larger series was reported in 1949 (Heath), but the period of observation was not of sufficient length to allow valid conclusions to be drawn as to the ultimate course of the disease. It is well known by those interested in the cancer problem that the number of survivors decreases with each five-year period of observation. It is this fact that makes a regular follow-up program of a single group, such as this, of such vital importance if we are to learn the true nature of this or any similar disease. The tendency for the disease to start as a localized process and later to become generalized is appreciated only by such long-term observations. It is this feature also which makes it impossible to speak of cures when one is reporting a series of patients with carcinoma. Rather, one can speak only of survivors living with or free of disease for a given period. In reporting deaths, it must be stated whether the patient died of the disease or from other causes, with or without known disease.

Biopsy.—Another important feature of Dr. McGavic's series is the fact that biopsies of all the lesions were made. This is essential for diagnosis, classification, and planning and evaluation of therapy. It is to be urged that biopsy be made of all tumors, no matter how typical they may appear clinically, for the only truly valid series are those in which microscopic examinations have been done. As new sites of involvement appear, biopsy of these, too, must be made, for lymphomas may vary in type from site to site. Biopsy affords the only true means of studying the course of the disease.

During the past six years at the Institute of Ophthalmology we have treated 32 patients with various types of ocular lymphosarcoma. Twelve were men and 20 women, with an average age of 59 years. The disease was located in the orbit in 23 cases, in 4 of which it was primarily in the lacrimal gland; in the subconjunctival tissues in 7 cases; in the lid in 1 case, and in the lacrimal sac in 2 cases. Biopsies were done on all patients, and the pathologic diagnosis was lymphocytic cell type in 14 and reticulum cell type in 12; in the remainder no cellular diagnosis was made. In 14 of the cases the ocular involvement was only part of a generalized process. In 18 cases there was no other evidence of the disease. The period of observation ran from 2 months to 6½ years, with an average of 27.3 months. This period is too brief to allow one to draw conclusions. However, in this period three have died of their disease and eight are known to be living with disease. In all these cases the ocular involvement was only part of a generalized process. None of the patients presenting ocular lymphosarcoma alone have as yet developed other manifestations of the disease. It is certain, however, that further observation will alter this situation.

Treatment.—The excellent response of these lesions to irradiation is well known and requires no discussion. The main concern with the ocular tumors is the protection of the uninvolved structures.

Lid: When only the lid is involved, the eye can be shielded without difficulty.

Conjunctiva: When the neoplasm involves the subconjunctival tissues, the problem of protecting the uninvolved portion of the eye becomes more difficult.

A 50-year-old woman with known generalized disease was first noted, on Sept. 11, 1952, to have a mass involving the left nasal bulbar conjunctiva of the left eye, which biopsy showed to be a lymphocytic cell lymphosarcoma. At that time she received 30 mg. of triethylene melamine, a form of nitrogen mustard, in divided doses, and x-ray therapy to the eye was delayed in order to observe the effect on

the ocular lesion of treatment with this drug. The tumors elsewhere regressed, but the conjunctival mass remained unchanged; therefore, on Feb. 9, 1953, the area was irradiated, the following factors being employed: 220 kv.; 20 ma.; 0.5 Cu plus 1.0 Al filters; 35 cm. T.S.D. to the lids and 50 cm. T.S.D. to the lacrimal sac and the nasolacrimal duct; 500 r to alternate portals twice a week for six times, making a total dose of 3,000 r X 2. The total dose was 2,000 r to the anterior portal and 3,000 r to the temporal portal. A plaster cast was made of the patient's face, and on this a lead shield was molded. By having the patient look to her left, the globe was protected by the central shield and only the tumor mass was irradiated.

Orbit: The incidence of orbital involvement in our cases is considerably higher than in other series. Orbital tumors are, however, amenable to therapy provided the globe is adequately shielded. Whether this tumor is more prevalent than formerly, or whether we are more aware of it, is unknown. However, according to Dr. A. B. Reese, in the pathologic files of the Institute of Ophthalmology in New York, lymphomas now rank second to hemangiomas as the cause of exophthalmos. A plaster cast of the patient's face is made and a lead mask prepared, as previously described. The area to be treated is outlined on the patient's face with eyebrow pencil and the mask cut accordingly. The exact type of cut-out and the direction of the patient's gaze will vary, depending upon the area to be treated. To date, none of the patients have shown any evidence of radiation injury to the globe with the doses and the shielding employed.

Summary.—Dr. McGavic has made an outstanding contribution to our understanding of lymphosarcoma, not only as it affects various ocular structures but in its relationship to the generalized process. I would again urge you to insist upon a biopsy and to follow your patients indefinitely whenever possible. Irradiation is the treatment of choice, and with adequate protection a satisfactory response can be anticipated.

Dr. Henry D. Diamond: I think we can reemphasize some of the points brought out both in Dr. McGavic's paper and in Dr. Merriam's discussion. First, about 7% of all recordable cancer falls in the region of the lymphoma and leukemia grouping. As you probably realize, as in all cancer, the most effective period in which treatment can be instituted is in the early, or localized, phase of the disease. I can restate a second fact that Dr. McGavic brought out, and that is that not infrequently any one of the particular histologic varieties, such as Hodgkin's disease, in the categories of paragranuloma, granuloma, or sarcoma and lymphosarcoma, beginning with giant follicle lymphoma and going all the way through diffuse lymphosarcoma and reticulum cell sarcoma, can be unicentric in origin. It is a well-known clinical observation that these diseases in time tend to disseminate, so that in our treatment of the disease we should attempt to make a clinical classification and assessment of the patient at the first observation of the case in terms of Categories I, II, or III: (I) those which fall into the category of unicentricity, without blood changes or other alterations; (II) early beginning generalizations, though still with regional localization of the disease, and, finally, (III) the universal category, in which all patients with leukemia will obviously fall. I would hold, indeed, that the treatment of choice in all varieties of lymphoma should be that of radiation—certainly, in Category I, in which, theoretically at least, cure is a possibility with adequate obliterative radiation therapy. All too often the clinician tends to treat just to the point of disappearance of disease tissue, even in patients who have unicentric or monofocal disease, without, therefore, giving the patient a chance of at least sterilization of the particular focus and long survival. I make this statement because in clinics where large numbers of lymphomas are seen, the patients who fall into the early, unicentric group are the ones who go on to have the largest five-year survival rate. At one time the theory was promulgated that perhaps the survival rate could be assessed from the point of view of the microscopic appearance of the tumor, to which Dr. McGavic made reference. I do not believe, however, this can be correlated with the clinical aspect, since in certain instances, irrespective of the type of disease or of the nature of treatment,

long survival has occurred, but oftener than not, irrespective, again, of the histologic nature of the tissue, if the process is still localized to a single focus, adequate radiation therapy may well produce long survival in the patient.

No reference has been made here to some of the chemical agents used in the treatment of this group, except for nitrogen mustard. As you realize, there is now a great field having to do with the chemotherapy of cancer. This plays an important role in the study and treatment of lymphomas and leukemias, where the testing of chemotherapeutic agents can be done most successfully, because at all times there is material at hand for biopsy, and the normal evolution of the disease can be studied with reference to the effect of a chemotherapeutic agent. Reference was made by Dr. Merriam to triethylene melamine, a nitrogen-mustard-like compound by virtue of its ethylene-imine moieties. Its value is that it is given orally, in contradistinction to nitrogen mustard, which must be given intravenously. In the leukemias we have another fruitful testing ground for chemotherapeutic agents. Here we have agents which are the antagonists of normal metabolic functions themselves, and so can be used successfully in acute leukemia. These agents are essentially the antagonists of purine or folic acid. Cortisone and corticotropin, which influence the hormonal environment of the cell, have been tried, successfully. The eye, in my opinion, is no different from any other part of the body with lymphoma, since lymphomas can occur anywhere in the body.

The Eye and the Orbit in Trichinosis. Dr. S. E. Gould, Detroit (by invitation).

Since the ophthalmologist may be consulted early in trichinosis, often as the first physician, it is important that he be familiar with the ocular manifestations of the disease. These manifestations are chiefly the result of invasion by the larvae of Trichinella spiralis of the extraocular muscles, their development and encystment in the muscles, and the accompanying edema and inflammation in the muscles and adjacent ocular structures. Common symptoms, often occurring early, include edema of the eyelids and conjunctiva, frontal or supraorbital headache, conjunctivitis, hemorrhage in the bulbar conjunctiva, and pain on movement of the eyeballs. Of frequent occurrence also are retinal edema, hyperemia, and short linear hemorrhages. In an epidemic of trichinosis involving 60 soldiers, reported by Schmidt (*Klin. Monatsbl. Augenh.* **110:** 73-79, 1944), linear retinal hemorrhages were seen rarely in mild infections (2 of 24) but in the majority of severe infections (21 of 36 patients). In 12 of 15 patients who died, such hemorrhages were seen during life. Their clinical detection, therefore, may be regarded as of prognostic value.

In the literature only two instances have been encountered in which a human eye has been microscopically studied in fatal trichinosis. In one of these (reported by Schmidt) iron deposits were present in the retina; these were believed to have been related to small retinal hemorrhages seen during life. The other, reported by Herrenschwand (*von Graefes Arch. Ophth.* **119**: 374-385, 1927-1928), showed conjunctivitis, heavy trichinous myositis of the extraocular muscles, minute retinal hemorrhages, and focal retinitis, and within 6 of 10 focal inflammatory areas in the retina a young Trichinella larva.

In an experimental study, we fed 4 rabbits and 13 white rats heavy or lethal doses of Trichinella larvae and histologically examined the ocular structures at various intervals up to 33 days after feeding.

In rats that died at two days of diarrhea, extreme dehydration was reflected in the ocular apparatus by drying of the secretions in the conjunctival sacs and by precipitation of the secretion of the lacrimal glands, as seen in section. Edema of the eyelids and conjunctivae in rabbits was observed and photographed during life. In the microscopic sections, edema was regularly noted and was frequently accompanied by inflammation, not only in the eyelids and conjunctivae, but also in the extraocular muscles, the connective tissues, and the choroid. The experimental findings indicate that, in addition to the extraocular muscles, the other ocular structures may be expected frequently to show pathologic changes in severe trichinosis.

DISCUSSION

DR. HAROLD W. BROWN: As Dr. Gould has pointed out, trichinosis is one of the most important public health parasitic diseases. He mentioned that approximately 25% of us are going to have this infection before we go to our graves. In New Orleans they found that 3.5% of the population were infected. In Rochester, N. Y., 17.5% of a series were found at autopsy to harbor the infection, and in Boston, 27.6%; in New York we recently had 84 cases in which the infection came, not from poorly cooked pork chops, but from the wursts. Here in New York this infection is due largely to the habit of people from Central Europe of eating prepared wursts and sausages without cooking. What is the chance of getting infected meat? In Philadelphia, Dickman (Dickman, A.: Trichinosis: Distribution of Trichinella Spiralis in Pork Products Sold in Philadelphia, *J. Lab. & Clin. Med.* **23:** 671-680; 1938) found that 1.6% of the pork chops and 9.5% of the sausages were infected. Schwartz (Schwartz, B.: Freedom from Viable Trichinae of Frankfurters Prepared Under Federal Meat Inspection, *Proc. Helm. Soc. Wash.* **6:** 35-37, 1935) found the Trichinella cysts in 1.0% of 1,118 frankfurters examined. You will see that we have here a real problem in public health. As ophthalmologists, we can diagnose it, but we have several other techniques which will help to confirm the diagnosis early in the disease. We have an intracutaneous test, and it is probably 90% accurate. It becomes positive about the 14th day, and a positive test on the 15th or 16th day is significant. We do not wait for the 14th day, because a negative test followed later by a positive test is most significant. At the New York City Department of Health we do a complement fixation test and a flocculation test; here, again, we do the tests immediately on suspecting the diagnosis, for a negative test turning to positive is very suggestive.

We have no specific chemotherapy, only supportive treatment. A number of years ago a piperazine compound was used, and it looked as though it might be of some value. We have been trying out a large number of piperazines on infected mice, and eventually one of them may prove to have some value; but you can see from Dr. Gould's slides that it is very difficult to get at the adult worm, which is embedded in the intestinal mucosa. That is our real problem.

Control is really very simple. All one has to do is to cook one's pork, and cook it thoroughly. Theoretically, sausage or wurst as it is obtained from the butcher is supposed to have been processed to kill the larvae, but practically this has not always been done. The real control consists in controlling the infection in hogs, and the way to do that is to cook the garbage fed to hogs; some 41 states have such a regulation, for it is through the eating of this 1.6% of pork chops and 9.5% of sausage scraps that the disease is spread from one hog to another. We know the diagnosis; we have no specific treatment, and what we have to depend on is individual control through cooking and mass control through the cooking of garbage. I noticed that Dr. Gould has a recent paper out suggesting the protection of pork through certain irradiative processes, which may be the final solution (Gould, S. E.; Gomberg, H. J., and Bethel, F. H.: Prevention of Trichinosis by Gamma Irradiation of Pork as a Public Health Measure, *Am. J. Pub. Health* **43**: 1550-1557, 1953).

DR. EDWARD BASSEN: Dr. Gould, it has been a great pleasure to listen to your presentation of what I should call a fascinating and intriguing subject. If 1,000,000 people become infected with trichinae yearly, and if the eye symptoms are the most prominent in 45% of the patients who manifest the disease, it behooves us to be on the lookout for this infection. I should like to present three cases which Dr. Perera and I have seen within recent years in our office. Those who were at the Eye and Ear Infirmary will remember this disease, for it was one of Dr. Verhoeff's favorite diagnoses. As young residents we used to be amazed, the first, second, or third time, by his looking at this characteristic periorbital edema and making the diagnosis of trichinosis. In these cases the blood cell count would show 40 to 60% eosinophiles. Once you have seen the very characteristic eye picture, you will never again miss the diagnosis.

In my medical student days we were still being taught that in a diagnostic problem one should think of syphilis. I suspect that nowadays a medical student never sees a case of syphilis, and I think trichinosis has taken its place as the chameleon of diseases. It can take the form of almost anything. If you would buy one of the bottles of patent medicine they used to sell 40 or 50 years ago and read the list of diseases which that magic cure-all would take care of, you would find listed there all the diseases which trichinosis can imitate. The literature on the subject is most varied. It is a moot question in theological schools whether the Mosaic prescription against the eating of pork was made because the ancient Hebrews actually knew about trichinae, and as yet it has not been settled. In 1950 *The New Yorker* had a fascinating article on trichinosis.

The first case was that of a man of 25 who came to the office complaining of swelling of his lids. He had no pains or aches, was not ill, and had what I call the characteristic appearance of periorbital edema. He had 44% eosinophiles but never presented any other symptom. Three months later he still had 35 or 40% eosinophiles, and then he disappeared. There were no localizing symptoms.

The second case, that of a woman of about 35, was a patient of Dr. Perera's. She came in with the characteristic edema, which was so severe that she had an actual exophthalmos of one eye. Dr. Perera sent her to her family physician. Her temperature was 103 or 104 F.; she was very ill and was admitted to the hospital. On the basis of a 45% eosinophile count, together with the ocular picture, the diagnosis of trichinosis was made. She had a very stormy time; she presented neurological and cardiovascular symptoms, with her temperature running to 104 F.; she was on the danger list for two weeks but finally recovered and is now well.

Dr. Birchell is here; at dinner he showed me a slide of encysted larvae in the deltoid muscle. Those of you who remember Dr. Ben Witt Key will recall that in 1930 he published in *American Journal of Ophthalmology* a case similar to that of Dr. Perera's. The exophthalmos was so pronounced that the patient was admitted to the New York Eye and Ear Infirmary with the diagnosis of orbital cellulitis secondary to sinus disease. An operation was to be done, but the x-ray was negative; during the interval a blood smear had been made, which showed 70% eosinophiles. On the basis of the eye picture and the blood cell count, surgery was postponed, a tentative diagnosis of trichinosis was made, and three days later a section taken from the deltoid was found to be positive for the larvae. This is the slide in Dr. Birchell's possession.

The third case is that of a woman of 35 who came to the office with what I call the characteristic eye picture, but she also had been feeling ill; she had pains and aches. On the basis of the eye picture, I called her family physician and said I thought she had trichinosis and asked him to examine her and to do a blood count. Apparently, he had never seen a case of trichinosis, and he decided she had the grip; so he gave he chlortetracycline (Aureomycin), penicillin, and streptomycin for a week; after that, her temperature having gone to 104 F., he began to question his diagnosis and did a blood cell count. She had 14% eosinophiles. She developed neurological symptoms, lost the use of her right leg, and was admitted to the New York City Hospital with the diagnosis of trichinosis. The neurological picture was so bizarre and confusing that they would not accept the admission diagnosis. They did repeated lumbar punctures and never got the same findings twice. The picture was confusing and nondefinitive; after she had been very sick for two weeks, they took a biopsy specimen of the deltoid muscle and found it to be positive for larvae. She was acutely ill for six weeks. The last time I saw here she was perfectly well.

DR. ALFRED ANGRIST: Dr. Gould, in closing, will you comment on our experience in a survey we did in our institution, where we found that about 30% of the population showed trichinellas in larval form in the diaphragm and that the highest percentage was in patients who should have obeyed the Mosaic law, but apparently had not.

DR. S. E. GOULD: The only reference I can give to Dr. Angrist's comment regarding the incidence of trichinosis in Jewish patients is the survey made by the

United States Public Health Service, with the cooperation of a great many hospitals throughout the country. In this survey, covering more than 5,000 autopsies, the average incidence of trichinosis was 16%, but in the patients known to be Jewish, the incidence of trichinosis was only 1%. In a clinical study on 3,000 hospital patients, we found that 6% gave an immediate skin reaction with a Trichinella antigen, while among 100 inmates in the Jewish Old Folks Home in Detroit, we found that only 1 gave an immediate positive skin test.

Concerning the value of the skin test, we conducted a clinicopathologic study of 388 cases in which we compared the skin tests during life with the finding of T. spiralis in the same persons at autopsy. Only 10% of those found to be harboring larvae in their muscles had given a positive skin test during life, while 5% of those in whom no larvae were found at autopsy had given a positive test during life. Therefore, the test has little value in indicating the presence or absence of old trichinosis. It is believed, however, that the immediate skin test is frequently of diagnostic value in recent trichinosis but that after a few years the skin loses its reactivity.

With respect to treatment, the only drugs that might be given with benefit are corticotropin and cortisone. Either of these should lessen the severity of the symptoms and may have a favorable effect on the course of the disease itself during its acute stage. If the severity of symptoms can be eased, a good deal will be accomplished for the comfort of the patient, and perhaps also for the outcome of the disease. After a day or two of treatment the aches and pains may subside and the patient may believe that he is on the road to recovery. However, if the medicament is discontinued, the pains may return in all their severity, and the patient then knows that he is not yet well and should remain under treatment. In severe infections it is important to confine the patient to bed until all danger from myocarditis has passed. The heart symptoms are likely to appear one or two weeks after the muscle symptoms begin to subside, and therein lies the danger of permitting the patient out of bed too soon. In moderately severe cases, therefore, it is well to keep the patient in bed and to take electrocardiograms at various times. We had a case in point. One of our supervising nurses entered the hospital after an illness of four weeks. The diagnosis was made on finding an eosinophile count of 62%. We put her to bed at absolute rest, under the care of nurses, day and night. She said it was silly to give her so much attention and that she was not so very sick. Ten days after she had been put on absolute bed rest, there developed palpitation, smothering sensations over the precordium, and significant electrocardiographic changes that had not been present previously. These symptoms and electrocardiographic changes persisted for 10 days, after which she recovered. Many a patient has died suddenly of heart failure after having been allowed to get out of bed after the muscle symptoms had begun to abate, in the belief that he was on the road to recovery.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Truman L. Boyes, M.D., *Chairman*

Charles A. Perera, M.D., *Secretary*

Residents Meeting, March 15, 1954

Ocular Tuberculosis. DR. GABRIEL GRECO (by invitation).

Crystals in the Anterior Chamber. DR. ELLIS GRUBER (by invitation).

The sparse literature was reviewed, and cases reported by Bonaccolto, Wendell Hughes, Koby, Knapp, Purtscher, Danielson, Scott, and Hubbersty and Gourlay were described.

The author presented three cases seen at the New York Hospital.

The first patient was a 75-year-old white man with a mature cataract in his left eye for over 19 years. He entered the hospital with acute glaucoma of this eye. The anterior chamber was of normal depth and was loaded with crystals. Vision was

limited to light perception. The cataract was removed after irrigation of the anterior chamber. Healing was uneventful. Corrected vision is now 20/40; the fundus is normal; the vitreous face is intact, and there is no synchysis scintillans.

The second patient was a 26-year-old man who had been admitted to the hospital in 1943, at the age of 15, with retinal detachment of his right eye following injury by a rubber ball the previous year. Two diathermy operations were performed, without success. One year later a cataract was noticed. In December, 1953, he observed that his right eye sparkled, especially in the light. Examination showed a normal left eye. The right eye was blind, with pupil fixed at 2.5 mm. The anterior chamber was deep and filled with shimmering, iridescent, needle-shaped crystals, which moved freely in the aqueous. There was also a pseudohypopyon of this material at the bottom of the chamber. The lens was opaque and its capsule seemed intact. The tension was 17 mm. Hg. The pupil dilated poorly, but enough to permit one to see that the lens was subluxated inferiorly and that crystals could be observed passing behind the iris in the upper nasal aspect.

The third patient was a 71-year-old white woman, known to have had a cataract in her left eye for eight years. There had been recurring attacks of pain and redness in this eye for one month. A diagnosis of iritis had been made, and atropine drops were instilled. When she was seen at the hospital, vision of the affected eye was limited to light perception; the pupil measured 3.5 mm. and was fixed, and the globe was congested. Slit-lamp study revealed diffuse corneal edema, a few K.P., moderate flare, and a few small crystals floating in the anterior chamber. Numerous small crystals were also seen on the anterior lens capsule. The intraocular pressure was 48 mm. Hg and was not altered by ingestion of 500 mg. of acetazoleamide (Diamox). Cataract extraction was performed. Recovery was uneventful. Seventeen days later, the vision was correctible to 20/40, the fundus appeared normal, and there were no crystals in the anterior chamber.

There seems to be no doubt that these crystals are composed of cholesterol. There are two theories regarding the origin of the crystals, with good evidence to support either concept; much would seem to depend on the individual case. One view is that the crystals originate from a degenerated and fluid vitreous and pass through the zonule into the anterior chamber. In favor of this view is the fact that many of the cases follow long-standing intraocular disease. According to the second theory, the crystals originate from a degenerated lens. In favor of this view is the fact that the author's three cases and most of those described in the literature have been associated with a mature or hypermature cataract. In those cases in which the cataract was removed the fundus appeared normal and there was no evidence of synchysis scintillans. The author was certain that the crystals were derived from the lens in his first and last patients.

A cataractous eye with crystals present in the anterior chamber suggests a rupture of the lens capsule, and this should be looked for in every case. If glaucoma is present, one should not hesitate to perform a cataract extraction as a primary procedure.

Bronchogenic Carcinoma with Metastases to the Iris. Dr. Merritt E. London (by invitation).

The patient was a 39-year-old Negro, admitted for the third time to the Veterans Administration Hospital, Bronx, N. Y., with the complaint of pain, redness, and loss of vision of his left eye for four weeks. Lung resection for epidermoid carcinoma had been performed seven months before. Eye examination at that time was negative.

Examination showed a normal right eye. Vision in the left eye was limited to light perception and projection. There was intense congestion. The aqueous was cloudy, with a large hyphema. A large, gray, vascularized cheesy mass projected into the anterior chamber from the superior angle. The hyphema cleared in a few

days. The iris was then seen to contain numerous small nodules with a deposition of white particles in the inferior angle. Enucleation was performed 16 days after admission. Pathologic examination revealed a small tumor in the ciliary body extending into the anterior chamber. The cytologic features were identical with that of the lung tumor. A smear of aqueous aspirated at operation showed tumor cells.

Mensuration of the Human Eyeball by X-Rays: A Modified Technique. Dr. William G. Everett (by invitation).

This paper represents a preliminary report on a project supported by the National Council to Combat Blindness, with x-ray equipment furnished by the Picker X-Ray Corporation.

The author's interest in this work was stimulated by the paper of R. H. Rushton (*Tr. Ophth. Soc. U. Kingdom* [Pt. 1] **58:** 136, 1938). The possibility of measuring the axial length of the eye independent of its refractive powers suggests numerous applications.

The technique is based upon the phenomenon that x-rays are visible to the dark-adapted eye. This knowledge antedated Rushton's work by some 40 years, having been reported by such observers as Edison, Roentgen, Dorn, Czellitzer, Hemstedt, and Nagel. The subject received little attention until 1932, when Pirie and Taft made independent observations. After these reports, Gifford and Barth, in 1934, reviewed the subject and made attempts to understand the mechanism involved. They restated previous studies of selective stimulation of the retina by means of slit-like apertures in front of the source of x-rays. Rushton, by the use of such slits, devised an ingenious, precise method of determining the axial length of the eyeball.

The technique consists basically of interposing a lead shield with a slit opening between the x-ray source and the eye of the patient. A plane of rays thus formed is projected toward the dark-adapted eye of the subject from the temporal side. This vertical plane of x-rays transects the eyeball at right angles to its anteroposterior axis. An equatorial section of the retina is stimulated, and the subject is aware of a yellowish-green circle of light. The displacement of x-ray beam toward the posterior pole of the eye causes the stimulation of increasingly smaller circles, with finally a point of light at the fovea. The distance from the anterior surface of the cornea to the fovea is read on a Vernier scale.

With Rushton's method, the x-ray source remains fixed and the slit moves freely in front of it. This introduces an error due to the divergence of the x-ray beam. The author reduces this error by his method of shifting the x-ray source and the slit together, thus maintaining a static relation between them.

Scleral Calcification. Dr. Karl Rubner (by invitation).

This paper will be published in full.

Complete Anophthalmos. Dr. Max H. Reif (by invitation).

After briefly reviewing literature on this congenital anomaly and its classification (primary, secondary, and degenerative) by Ida Mann, the author presented a case of bilateral anophthalmos to add to the 70 or so previously reported. Clinically, it is very difficult to distinguish between primary anophthalmos and high degrees of microphthalmos.

On Oct. 8, 1953, Mrs. M. D., aged 34, had a spontaneous normal delivery of a premature female infant, weighing about 2,000 gm. The patient had four other children, three born prematurely and one at full term. All were born by normal spontaneous delivery and had no signs of any deformity. The mother, on admission, showed an Rh-negative blood with mild anemia.

The infant, on immediate examination, was found to be normal except for its inability to open the eyelids. The Coombs test for hemolytic disease of the newborn was negative. On the second day, when the pediatric resident attempted to make

an examination for retrolental fibroplasia and could not perceive any eyes, ophthalmic consultation was requested.

Ophthalmological findings were as follows: The head of the child was of normal contour and measurements. The orbits and lids were well formed and of normal size. The lids of both eyes closed and appeared sunken into the sockets. They could easily be separated. The palpebral fissures appeared to be of normal length, as compared with those of a premature infant of this child's weight, and there were no adhesions, which are usually present in anophthalmia, at the fornices. The cilia were present but scanty. The lacrimal puncta were noted. The lids were then separated with lid retractors; only the conjunctiva could be perceived. There were no signs of inflammation, or any purulent discharge, such as has been noticed in many cases. The sockets were then palpated with the small finger for masses, for fibrous tissue, for cysts, and for rudimentary pedicles, but none could be found. No other bodily abnormality could be located. The infant took nourishment well and gained weight during its five-month stay at the hospital. At the time of discharge a further examination of the sockets did not reveal the presence of any masses. From these findings, a clinical diagnosis was made of complete primary bilateral anophthalmia.

Endophthalmitis Phacoanaphylactica Following Penetrating Diathermy. Dr. Dahar Cury Jr. (by invitation).

This paper will be published in full.

Ocular Symptoms Following Severe Head Injury. Dr. Conrado P. Banzon (by invitation).

The patient, a 54-year-old white woman, was examined two and one-half years after she had suffered a severe cerebral concussion in an automobile accident. There were no skull fractures. The ocular findings included loss of voluntary ocular movements in the absence of any paralysis, loss of binocular fixation and conjugate movements, blepharospasm associated with twitching of the facial muscles, diminution of visual acuity with negligible fundus changes, and binocular diplopia. These manifestations were believed to result from injury to supranuclear centers and pathways.

Ocular Findings in Cerebral Palsy. Dr. Arnold S. Breakey (by invitation).

Cerebral palsy is an injury to the motor centers of the brain resulting in neuromuscular disability. It is divided into three major types: spastic, with lesions in the motor cortex or the pyramidal tracts; dyskinesia, with lesions in the basal ganglia, and ataxia, with lesions in the cerebellum.

There are about 125,000 cases up to the age of 20 in the United States, making cerebral palsy second only to poliomyelitis as a crippler of young people. Little or nothing has been written on the ocular status of this group.

One hundred unselected patients from the Cerebral Palsy Clinic at Lenox Hill Hospital were examined and followed for two years. The following ocular abnormalities were found:

Normal	44%
Esotropia	40%
Exotropia	8%
Optic atrophy	3%
Congenital cataracts	2%
Coloboma of iris	1%
Paresis of upward gaze	1%
Spastic lids	1%
	100%

Concurrent conditions

Nystagmus	2
Papilledema	1

With respect to the eyes, normal and pathologic cases were distributed among the three major cerebral palsy groups. Without a guide to the care of such cases, generally accepted ophthalmological principles for the management of extraocular muscle problems were followed.

Among the tropia cases, (1) relatively small (+2) spheres relieved significant amounts of esotropia; (2) atropine for occlusion was extremely useful in developing alternators and in preventing amblyopia; (3) in a fair number of cases improvement occurred spontaneously with age as binocular experience increased; (4) surgery was successful in cases in which the deviation was relatively fixed and constant.

Taken as a group, the cases of optic atrophy, congenital cataracts, and coloboma of the iris represent an incidence of 6%. This group may be considered as one of congenital anomalies, the incidence of which is much higher than would be expected in the normal population.

Nystagmus did not represent a serious problem, and none of the cases occurred in the ataxic group with lesions in the cerebellum.

Gross visual field defects were not found.

One case of paresis of upward gaze and a case of spastic lids were noted. Papilledema was incidental to an astrocytoma in one case.

Cerebral palsy victims in our population represent a very significant numerical group. Their ocular status has been largely ignored because of more obvious and limiting defects. Each one deserves a careful examination and follow-up. Adherence to accepted ophthalmological principles, with a few modifications as noted, yields gratifying results.

Keratitis Sicca—Problems and Management. Dr. Norman Yourish and Dr. Nathaniel C. Wollin (by invitation).

Surgery of the Inferior Rectus Muscles in Divergent Strabismus. Dr. William B. Shekter (by invitation).

Elevation of Intraocular Pressure Caused by Steroid Therapy in Sarcoid Uveitis. Dr. Robert W. Collier (by invitation).

Two of the three patients reported were 14-year-old Negro children with sarcoid uveitis. The third patient was a 29-year-old Puerto Rican woman.

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Midwinter Clinical Meeting of Pennsylvania Academy of Ophthalmology and Otolaryngology.—The Fifth Annual Midwinter Clinical Meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held at the Eye, Ear, Nose and Throat Hospital in Pittsburgh, on Wednesday, Jan. 19, 1955.

This one-day meeting will consist of operative clinics and symposia. Arrangements will be made for the 1955 meeting in the Hotel Traymore, Atlantic City, N. J., May 18 to 21, 1955.

Gill Memorial Eye, Ear and Throat Hospital.—The Gill Memorial Eye, Ear and Throat Hospital, in Roanoke, Va., will hold its 28th Annual Spring Congress in ophthalmology and otolaryngology and allied specialties, April 4 to 9, 1955.

Among the guest speakers who will attend are the following:

DR. HENRY L. BIRGE.....Hartford, Conn.	MAJOR GEN. DANIEL OGLE Washington, D. C.
DR. PAUL BOEDER.....Southbridge, Mass.	DR. THOMAS PAINE.....Ann Arbor, Mich.
DR. WILLIAM B. CLARK.....New Orleans	DR. R. TOWNLEY PATON.....New York
DR. DAN M. GORDON.....New York	DR. JAMES PURNELL.....New York
DR. ANDERSON C. HILDING....Duluth, Minn.	DR. ALBERT D. RUEDEMANN.....Detroit
DR. CHEVALIER L. JACKSON....Philadelphia	DR. ROBERT E. RYAN.....St. Louis
DR. BERTHA S. KLIEN.....Chicago	DR. RICHARD SCHNEIDER...Ann Arbor, Mich.
DR. T. G. MARTENS.....Rochester, Minn.	DR. JOHN SHELDON.....Ann Arbor, Mich.
DR. DANIEL S. MILLER.....Boston	DR. GRANT WARD.....Baltimore

SOCIETY NEWS

All-India Ophthalmologic Society.—The All-India Ophthalmologic Society will hold its annual meeting Feb. 16 to 19, 1955, in Bombay, India.

In behalf of Dr. S. N. Cooper, secretary of the society, a cordial invitation is extended to United States ophthalmologists and their families to attend the meeting and to take part in the scientific phase of this conference. The symposium for the 1955 conference will be on "Diseases of the Lacrimal Apparatus." However, papers on other ophthalmologic subjects may also be read.

The Ansett Travel Service, 323 Geary St., San Francisco, is in charge of all travel arrangements. The tour will originate in San Francisco, take six weeks, and include stopovers in Honolulu, Tokyo, Hong Hong, Bangkok, the Taj Mahal, New Delhi, Bombay, Cairo, Rome, and New York.

The all-inclusive costs, including first-class air transportation, meals, hotels, and excursions will be $2,800 per person.

Bowman Lecture.—The Bowman Lecture, which is presented at the meeting of the Ophthalmological Society of the United Kingdom, will be given by Dr. John H. Dunnington, Director of the Institute of Ophthalmology, Presbyterian Hospital, New York, in London, England, on April 28, 1955.

Books

Behandlung von Augenkrankheiten. By Alfred Bangerter. Price, $4.00. Pp. 112, with 15 illustrations. Hans Huber, Marktgasse 9, Bern; exclusive representative for U. S. A. and Canada, Intercontinental Medical Book Corporation, 381 4th Ave., New York 16.

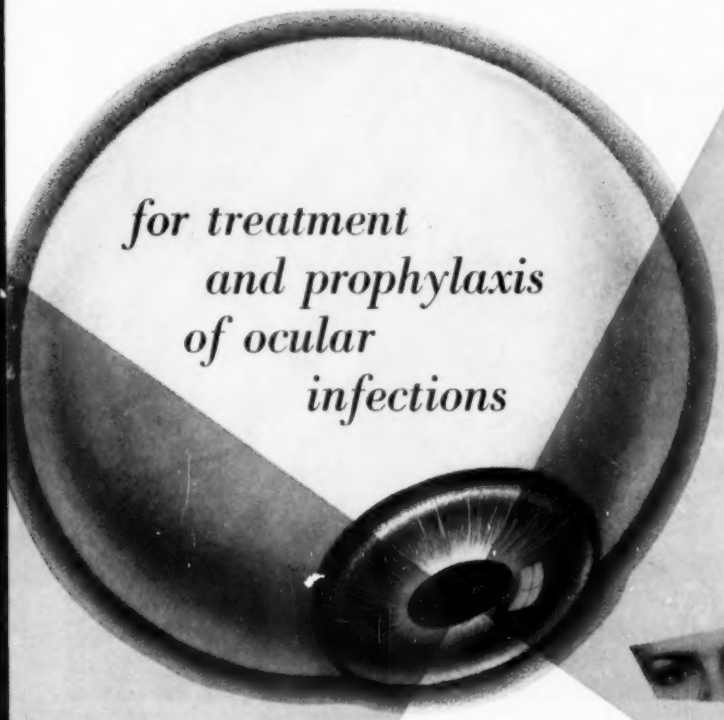
This volume gives a short account of office treatment for the general practitioner, in German. Since there are a number of similar texts in English, it will have little interest for the general practitioner in this country. Its contents have been well selected, and the illustrations are good.

Peripheral Circulation in Man. By G. E. W. Wolstenholme and Jessie S. Freeman, assisted by Joan Etherington. Price, $6.00. Pp. 219, with 72 illustrations. Little, Brown & Co., 34 Beacon St., Boston, 1954.

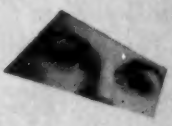
This volume is a compilation of the papers presented by those attending a symposium on the Peripheral Circulation in Man held May 11 to 13, 1953, and promoted by the Ciba Foundation. While not directly touching on the ocular circulation, the book covers the methods for studying blood flow and changes in circulation due to exposure to cold or heat, the action of epinephrine and arterenol on blood flow, the neurohistology and reflex control of the general circulation, and the effects on it of sympathectomy. Other subjects dealt with are the cold agglutinins and the influence of visceral activity on the peripheral circulation. The book will, therefore, be of value to those in ophthalmology who are doing research on the ocular circulation.

Observations on Hole in the Macula. By Paul Tower. Price, $2.00. Pp. 60, with 15 illustrations. S. Karger, Ltd., Holbeinstrasse 22, Basel, Switzerland, 1954.

This brochure is a historical review of the subject of macular holes, their etiology and pathology. The author concludes that small holes, which are asymptomatic, occur frequently and seem to be on the increase. Senile degenerative processes are of great significance in the causation of macular holes without a relevant history of trauma. The holes themselves represent a terminal stage of various pathologic processes. Trauma may either cause a mechanical tearing of the retina or lead to cystoid degeneration, which, according to Tower, is the most frequent precursor of hole in the macula. The older view that cystoid degeneration is the exclusive precursor of macular holes is rejected by the author. The ophthalmoscopic appearance of various types of holes is described. The author calls attention to the fact that the punched-out margin of macular holes should no longer be considered typical of all holes. In those cases in which perifoveal edema is concomitant with a beginning hole in the macula, the use of retrobulbar injections of tolazoline (Priscoline) is sometimes dramatically effective.



for treatment and prophylaxis of ocular infections



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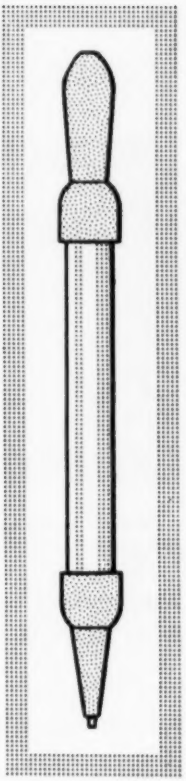

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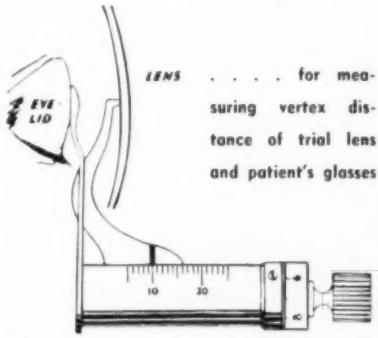

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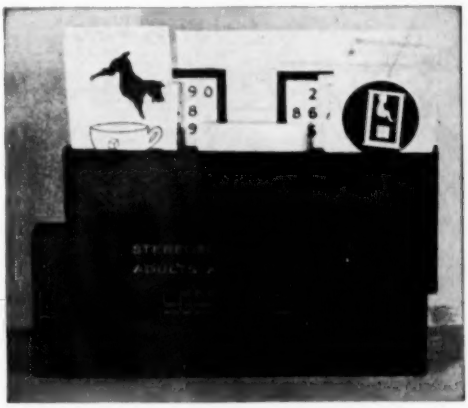

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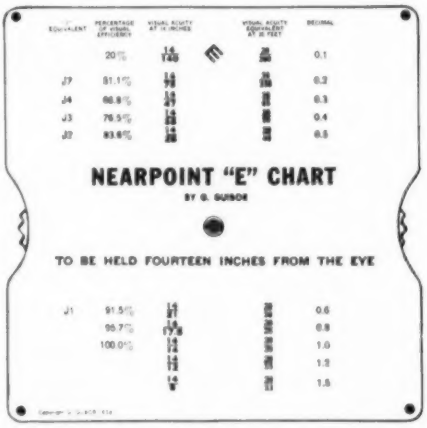

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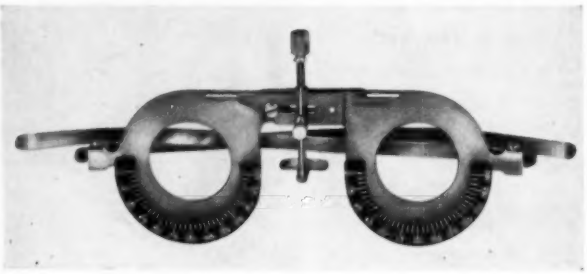

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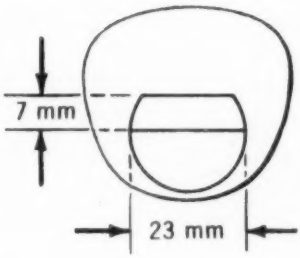

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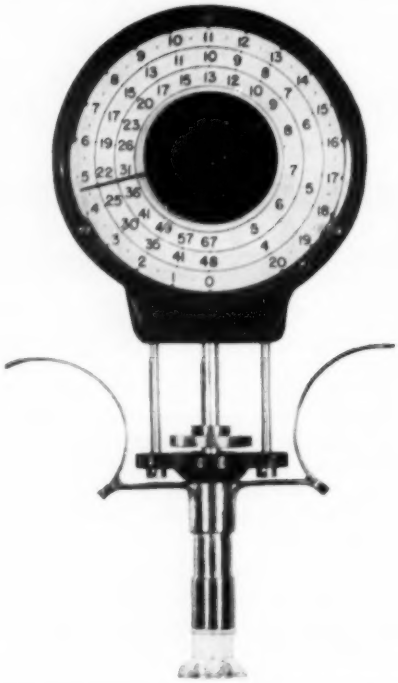

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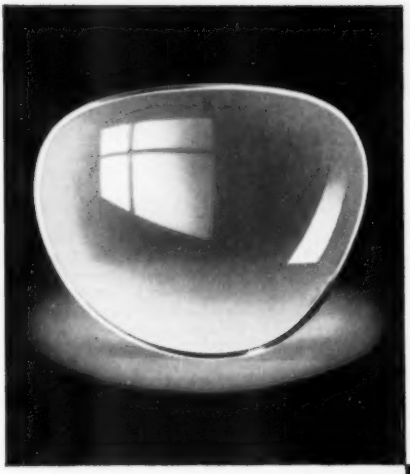

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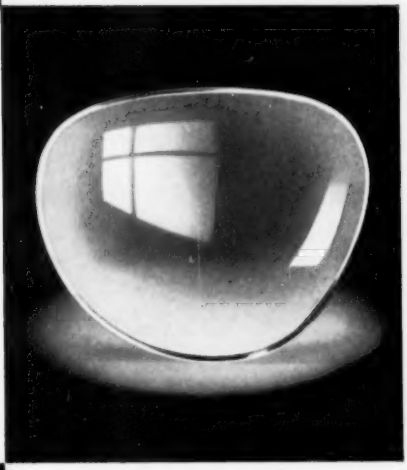

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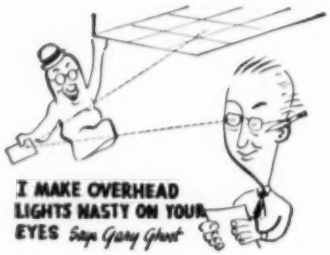

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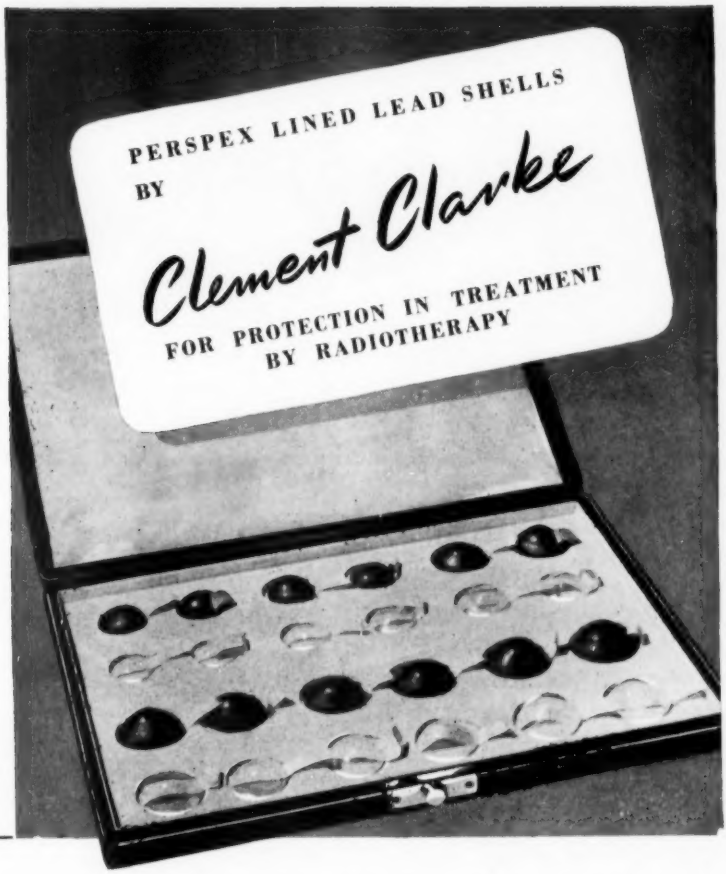

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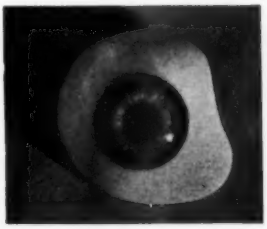

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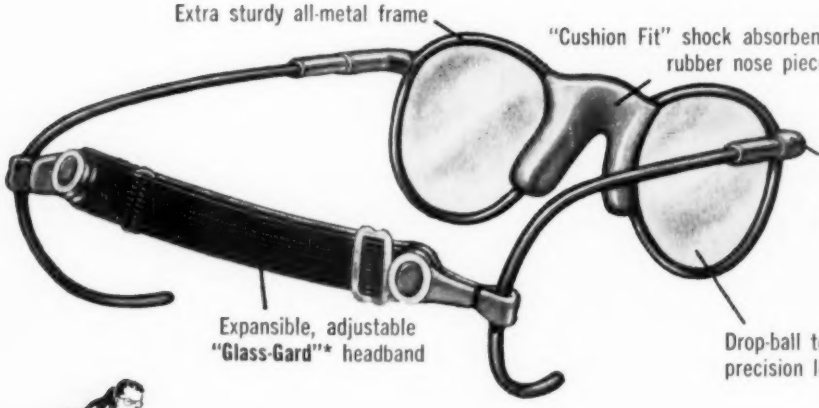
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